

# Retrospective: Frederic M. Richards (1925-2009)

BY JAMES V. STAROS

**F**rederic M. Richards, former president of the ASBMB and the Biophysical Society, passed away at his home in Guilford, CT on January 11<sup>th</sup>. He was 83.

Fred Richards was a towering figure in protein chemistry, having played a key role in moving the concept of proteins from amorphous colloids to discrete molecular structures. His contributions to protein science ranged from his central role in founding what is now known as structural biology—both experimental and computational—to the design and application of new chemical reagents for probing protein structure and function.

Richards was born on August 19, 1925 in New York City. After his graduation from Phillips Exeter Academy, he matriculated at the Massachusetts Institute of Technology (MIT). Military service intervened toward the end of WWII, but he returned to MIT after his discharge and received a B.S. degree in 1948. For his graduate study, he moved to E. J. Cohn's department at Harvard Medical School, where he worked with Barbara Low and received a Ph.D. in 1952. He stayed at Harvard for a year as a research fellow with Cohn and then moved to the Carlsberg Laboratory in Denmark, where, with Kaj Linderstrøm-Lang and others, he began working with ribonuclease. After a short stint at Cambridge University as a National Science Foundation postdoctoral fellow, Richards joined the faculty of the Department of Biochemistry at Yale University in 1955 as an assistant professor. He rose rapidly through the ranks, becoming professor in 1963.

In 1963, Richards was appointed chairman of the Department of Molecular Biology and Biophysics at Yale, which entailed a move from the Medical School to the Yale College campus. Richards spent a sabbatical at Oxford University from 1967 to 1968, for which Richards



and his wife Sally sailed their own boat with a small crew across the Atlantic Ocean.

Following this break, when Yale merged the Medical School Department of Biochemistry and the Yale College Department of Molecular Biology and Biophysics to form a new university-wide Department of Molecular Biophysics & Biochemistry, Richards became its founding chair (1969–1973).

Summarizing Richards' contributions to protein science is difficult because of the breadth that he covered. Much of the early work in Richards' laboratory focused on bovine pancreatic ribonuclease, and in particular a preparation that he discovered while in Linderstrøm-Lang's laboratory, dubbed ribonuclease-S (RNaseS). Richards and co-workers purified

and characterized RNaseS, separated it into S-peptide (residues 1–20) and S-protein (residues 21–124), both enzymatically inactive, and showed that S-peptide did not retain an ordered structure in solution but could be reconstituted with S-protein into enzymatically active RNaseS. They crystallized RNaseS and showed that RNaseS was enzymatically active in the crystal, putting to rest the widely held view (at that time) that protein crystal structures were irrelevant to the conformation and behavior of enzymes in solution. In collaboration with the late H. W. Wyckoff, they solved the structure to atomic resolution (a tie for the third protein structure ever solved to atomic resolution) with and without bound nucleoside monophosphate. While on sabbatical at Oxford, Richards designed and built the Richards Optical Comparator, better known in the field as "Fred's Folly," or simply "the Folly," which remained the method of choice for converting electron density maps to models, until it was supplanted by computer graphics.

The Richards Lab always included a "wet" component

focused on the properties of proteins in solution and on the design and application of new chemical reagents for modifying proteins in ways that reported on the proteins' structure and/or function. Types of reagents pioneered in the Richards laboratory included hydrophilic and hydrophobic photoactive reagents for studying membrane protein topology, cleavable cross-linking reagents for studying protein quaternary structure, and reagents that exploited the remarkably strong binding between ferritin and avidin for use in localizing target proteins within cellular structures.

Richards received many honors for his scientific achievements, including the Pfizer-Paul Lewis Award in Enzyme Chemistry (1965), a Guggenheim Fellowship (1967-1968), election as Fellow of the American Academy of Arts and Sciences (1968), election to the National Academy of Sciences (1971), the Kai Linderström-Lang Prize in Protein Chemistry (1978), the ASBMB Merck Award (1988), the Stein and Moore Award of the Protein Society (1988), and the State of Connecticut Medal of Science (1995).

What should not be overlooked in reviewing Richards' science is that the Richards Lab was a wonderful place to develop as a scientist, whether one's experience there was as an undergraduate student, graduate student, postdoctoral fellow, or sabbatical visitor.

We extend our sympathies and thoughts to Richards' family and friends. Below, as a tribute, we offer thoughts and reflections from several of his friends and former colleagues.

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*When I came back to the U. S. after doing my D. Phil. and postdoc in Europe, Fred Richards went out of his way to help me get integrated into the American structural biology community. It was typical of the man; over the years, he was enormously kind and supportive, not just to me, but to numerous young scientists. Since we worshipped him for his direct manner and extraordinary creativity, his support and friendship over the years meant more than I can easily express. Fred was a role model for how to behave, not just as a scientist but also as a person. I'm really going to miss him.*

**Gregory A. Petsko,**  
Gyula and Katica Tauber  
Professor of Biochemistry  
and Chemistry and Chair,  
Department of Biochemistry,  
Brandeis University

*In 1979, Fred was the incoming President of ASBMB (ASBC at that time) and chaired the search committee for recruitment of a new Executive Officer. While not excluding a scientist for the position, Fred did not exclude a non-scientist from consideration for the job. From a purely selfish view, I will be forever grateful for this decision and the trust he and the rest of the committee put in me. Fred was always someone who was enthusiastic about life, especially when he discussed sailing, and I will always remember him fondly. A personal loss and a loss to science.*

**Charles C. Hancock,**  
former ASBMB executive director

*Fred was very inclusive. He came from a family of strong women and married another strong woman. Sally and I recall his joking at his retirement party about the effect that this environment had on his development. He had a gift for mentoring women; setting an example himself through his creativity, work ethic, and high standards; and opening doors that might otherwise have remained closed. His choice of John Mouning as his right-hand man and his inclusion of John's wife, Thelma, and their children in lab activities, placed an African-American family in a prominent position in the scientific world and undoubtedly encouraged others to pursue careers in science.*

**Norma M. Allewell,**  
Dean of Chemical and Life Sciences  
and Professor of Chemistry and  
Biochemistry at the University of Maryland

*Fred Richards was an inspiration to me and other structural biologists of my generation. He had deep understanding of protein chemistry and structure. His presentations were crisp, delivered with a square-jawed assurance often punctuated by good jokes, frequently at his own expense. Among his historic findings was, with Flo Quijcho, that enzymes are active in the crystalline state as well as in solution. This all but silenced the frequently voiced biochemical concerns of the 1960s that crystalline proteins are somehow different from those in solution. Another was his finding that the cleaved S peptide of ribonuclease A binds to the rest of the protein, restoring native activity. This was a paradigm-defining result on protein-protein interactions.*

**David Eisenberg,**  
Director UCLA-DOE Institute  
for Genomics and Proteomics

*Fred Richards was such a remarkable person that it is difficult to describe his achievements in only a few words. He was an amazing experimentalist. As an undergraduate at Yale, I had a wonderful time building instruments for Fred, most of them related to the study of protein structure and dynamics in crystal lattices. One instrument we built allowed the measurement of the size of solvent channels in protein crystals, work that I believe influenced Fred's pioneering theoretical work with B. K. Lee on protein accessible surface areas. Fred also did pioneering work on enzyme mechanisms with Ribonuclease-S and nurtured an environment within the Yale WERMS group that led to a host of additional important discoveries in molecular structure and biophysics by colleagues and students. Fred motivated several generations of scientists, many of whom are still basically working on questions that he asked first. He will be missed by everyone who knew him.*

F. Raymond Salemme

*Fred Richards was a new assistant professor when I was a graduate student at Yale in the 1950s. Just back from his postdoc in Denmark, he brought to the Biochemistry Department new ways of looking at proteins, an infectious attitude that research was indeed fun, and a collection of elegant glass micropipettes, the first we had ever seen. We could not know it then, but he also brought with him the profound changes in scientific outlook that fueled the last half century of biology.*

Maxine Singer,  
Carnegie Institution, president emerita

*Whether it is ribonuclease, crystallography, folding, energetics, packing, solvent accessibility, or inside versus outside, Fred Richards was there. Much of present day research on protein bears the imprint and the impact of his creative studies. For more than 50 years, he produced a steady stream of bold and imaginative investigations that combined novel tools and approaches leading to invaluable knowledge of protein structure and function. He raised questions that had not been considered previously and devised experiments to answer them. In addition, Fred Richards was a remarkable teacher and citizen whose contributions as editor, head of the Jane Coffin Childs Memorial Fund for Medical Research, and President*

*of the American Society of Biological Chemists were incalculable. Moreover, he was an accomplished sailor and a great guy.*

Howard K. Schachman,  
professor of Molecular and Cell Biology,  
University of California at Berkeley

*One of Fred's outstanding characteristics was his penetrating, almost prescient vision and his ability to see far beyond the experiment at hand. One example: In a paper published in the JBC half a century ago (Richards & Vithayathil [1959] JBC 234: 1459-1465), in which were described the separation of ribonuclease S into enzymatically inactive S-protein and S-peptide and the reconstitution of enzyme activity by the re-association of S-protein and S-peptide, he observed, "The strength of the interaction in this enzyme system appears to be of the order of magnitude that might be required to explain the initial effects of peptide hormones in the target organs." As someone who has spent much of his scientific career working on receptors for one class of polypeptide hormones, I find this remarkably visionary—and typical of Fred.*

James V. Staros,  
professor of Biochemistry and  
dean of the College of Arts & Sciences,  
SUNY-Stony Brook

*I recall Fred with great affection. He was a marvelous mentor (although I was always a little in awe of him), a great scientist with whom one could discuss a whole range of phenomena (for example, the diffusion of ligands into proteins and protein crystals), and most of all, a person who made science and the life of science great fun.*

Louise Johnson,  
Sir David Phillips professor of Molecular  
Biophysics at Oxford University

*Fred was an original. He was one of the great protein chemists at a time when protein chemistry was center stage. His contributions were enormous.*

Ralph Bradshaw,  
professor of Chemistry and Pharmaceutical  
Chemistry and deputy director, Mass  
Spectrometry Facility,  
University of California, San Francisco