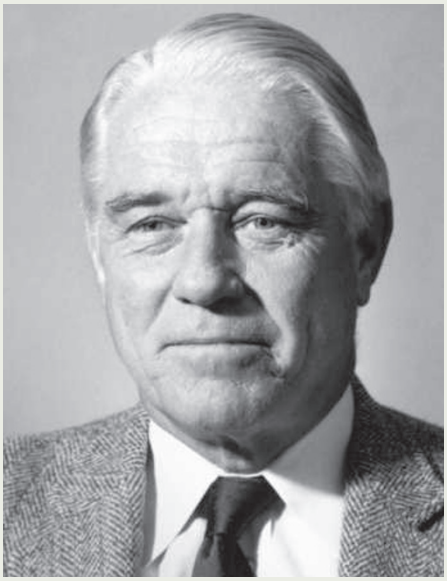
OBITUARY

Frederic Richards (1925–2009)

Pioneer in studies of protein structure and function.



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Frederic M. Richards, a leading light in the development of structural biology, died on 11 January at the age of 83.

Richards was a seminal figure in protein science, having had a key role in shaping our fundamental understanding of protein structure and function. His contributions ranged from the early use and development of protein crystallography, to computational analysis of protein geometry, and to the development of chemical probes for the analysis of membrane proteins. Remarkably, throughout his career many of his most influential contributions stemmed from work carried out with his own hands.

Richards came from old New England stock. His undergraduate education at the Massachusetts Institute of Technology was interrupted by service in the army during the Second World War, and was followed by a PhD degree at Harvard Medical School. His first and perhaps most striking contribution began in 1955, during his time as a postdoctoral fellow with Kaj Linderstrøm-Lang at the Carlsberg Laboratory in Copenhagen, and continued after he joined Yale University — where he would remain throughout his scientific career.

Pancreatic ribonuclease A, an enzyme that degrades RNA, was a favoured protein for study in the 1950s. Richards discovered that it could be cut into a short 'S peptide' and a larger 'S protein', which together were termed ribonuclease S and maintained enzyme activity. When these components were separated, each lost all enzymatic activity. But, surprisingly, they could be mixed together to reconstitute the active enzyme, demonstrating that a protein's chemical sequence contains the information needed to attain its active conformation. This work foreshadowed the more extensive refolding studies of ribonuclease A carried out by Nobel laureate Christian Anfinsen. Richards used chemical modification of S peptide to examine the contributions of the amino-acid sequence to the thermodynamic stability of the ribonuclease S complex — all long before the advent of peptide synthesis and site-directed mutagenesis made these types of study widely fashionable.

Together with Harold W. Wyckoff and others, Richards solved the X-ray crystal structure of ribonuclease S and examined the structure with a bound nucleoside monophosphate — this was the second enzyme structure to be solved, and the first protein structure solved in the United States. The relevance of a protein's crystal structure to its conformation in solution was a serious concern in the early days of protein crystallography. Richards's group established that the ribonuclease S protein was enzymatically active within the crystal, largely putting this issue to rest.

The complex conformations seen in the earliest protein crystal structures were a surprise. Early on, before such crystals were obtained, proteins were believed to be colloidal in nature, and after protein crystals were identified they were expected to display highly symmetrical structures akin to fibrous proteins. Richards developed computational tools to investigate the packing within proteins, leading to the discovery that a protein's core is as well packed as organic molecules in molecular crystals such as table sugar. Richards developed the calculation of the solvent-accessible surface area in proteins and used it to characterize their folding, assembly and function. Numerous investigators have adopted these tools for an ever-expanding variety of applications.

While on sabbatical at the University of Oxford, UK, in 1968, Richards designed and built what became known as the Richards Optical Comparator (or the Richards box), better known in Oxford as Fred's Folly, or simply the Folly, in part because of its architectural similarity to a gazebo. The device contained a half-silvered mirror that allowed the image of a wire model of a protein to be seen floating in the electron-density contour maps determined by X-ray crystallography and drawn on a set of stacked plastic sheets. The Folly permitted the wire model to be manually fitted to the electron density and was quickly adopted by protein crystallographers around the world; it was supplanted only by the advent of molecular-graphics software. My abiding memory of Fred Richards is the grin on his face when I showed him the alamethicin crystals I had grown for my PhD thesis, and his look of pride on seeing the version of the Richards box that I had built to fit the alamethicin model.

The Richards laboratory was a marvellous place for students, postdoctoral fellows and visiting faculty — usually limited to half a dozen, highly independent members pursuing widely disparate projects attacking some fundamental aspect of protein science. Despite the many demands on his time, his office door was always open for energetic and educational scientific discussions. Richards's enthusiasm for protein science was legendary — as were his passions for sailing and ice hockey.

Yale's Department of Molecular Biophysics and Biochemistry was formed by a merger of existing departments. As founding chair, Richards proved to have a deft touch on this difficult exercise, and showed great insight in hiring an outstanding cadre of junior faculty. The department was remarkable in the breadth of training it required of its graduate students, from molecular biology to molecular biophysics — all long before protein expression allowed both groups to work in the same area.

Richards also played a significant part in many science-policy issues, including his support for the Protein Data Bank (PDB), which was established in 1971 as a site for the voluntary deposition of macromolecular structures and experimental data. Richards led an early steering committee for the PDB and in the mid-1980s was head of an ad hoc committee that successfully encouraged journal editors to require structures reported in their pages to be deposited in the PDB. Richards's committee also succeeded in convincing the US National Institutes of Health to require the deposition of protein coordinates for continued funding. These policy shifts were not without controversy at the time, but their success ultimately facilitated the research of innumerable protein scientists. The timing was crucial, because it put the requirement for deposition in place just before the explosion in the number of structure determinations.

Further insight into Fred Richards's many contributions, and the joy he had making them, can be found in his own words in 'Whatever happened to the fun? An autobiographical investigation', published by the *Annual Review of Biophysics and Biomolecular Structure* in 1997.

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