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Henry F. Epstein, M.D. (1944–2013)

Family members, friends and colleagues of Henry F. Epstein were deeply saddened to learn of his untimely death from liver cancer on February 2, 2013. Henry's contributions to biological research spanned a wide range of disciplines and his personal influence guided the careers of a diverse group of people. Constant hallmarks of his persona were a tireless defense of basic biological research, an aversion towards dogma and an intrinsic sense of scholarship throughout his life.

Henry was born in the Bronx, New York in 1944 and followed the advice of his father, a civil engineer, to pursue a higher education. His mother was ever supportive and proud of his choices and preceded him in passing by only a few years. He graduated from Columbia University, New York and went on to obtain his medical degree from Stanford University, CA in 1968. At Stanford, Henry's sense of curiosity towards unresolved questions in medicine led him to the laboratory of Dr Lubert Stryer, where his interest in the relationship between basic protein structure and function was started. With Stryer, he used fluorescence spectroscopy to demonstrate that proteins are not rigid structures. Rather, they undergo 'breathing' movements, as shown with hemoglobin, and can display substantial flexibility, as shown with antibodies. Asking medically inspired questions led him to seek and make contributions with scientists who were true pillars of basic biological research. This theme was repeated throughout his life and was one he emulated as a mentor himself.

Largely owing to the rewarding experience with Stryer, Henry decided not to pursue clinical training and took a post-doctoral position with Christian Anfinsen at the National Institutes of Health, Bethesda, MD in 1969. By then, Anfinsen and colleagues had already performed the famous experiments with bovine pancreatic ribonuclease, demonstrating that all folding information is contained within the primary amino acid sequence of the protein. The primary questions within the protein-folding field concerned the pathways used by polypeptides to achieve their native state. Using nuclear magnetic resonance and fluorescence spectroscopies, Anfinsen, with Henry and Alan Schechter, observed that the unfolding and refolding of staphylococcal nuclease does not occur through a simple 'two-stage' process (in which the enzyme is either folded or unfolded). Rather, some amino acid residues become perturbed before the major cooperative transition, thus demonstrating the existence of protein-folding intermediates. These intermediates are now known to populate the folding pathways of many proteins during their biosynthesis in the cell, and are the substrates of a class of proteins known as molecular chaperones – a field of study

that eventually became the primary interest of Henry's research program.

During a visit to England in 1970, Henry arranged for a meeting with Sydney Brenner and Francis Crick and was offered a second post-doctoral position in the MRC Laboratory of Molecular Biology. He arrived in Cambridge in 1971 and worked on a project on *Caenorhabditis elegans* body-wall muscle under Brenner. At a time before DNA sequencing and recombinant DNA technology, Henry identified the product of the *unc-54* gene as a myosin heavy chain, and made the then-surprising discovery that there was significant redundancy for myosin genes in the worm, as in most eukaryotes. As a side project, he identified the first temperature-sensitive mutant in *C. elegans* (in *unc-45*). He speculated then that its activity would be related to a myosin assembly function. Brenner's influence as a polymath and his scientific approach of combining molecular genetics with biochemistry permeated the rest of Henry's career. While in Cambridge, Henry also reaffirmed his passion for rowing and discovered the value of casual meetings among scientists, both of which he cultivated for the rest of his life.

After Cambridge, Henry returned to the United States and ran successful research programs at Stanford University, Baylor College of Medicine, Houston, TX and finally as chairman of the Department of Neuroscience and Cell Biology at the University of Texas Medical Branch (UTMB) in Galveston, a position he held until his death. An early focus of his career as an independent investigator was to understand the biological consequences of myosin heavy chain multiplicity. He demonstrated that conventional myosin molecules are always composed of two identical heavy chains, and that these assemble differentially along the thick filament. Henry's laboratory also contributed to the identification of the genetic abnormality responsible for myotonic dystrophy (type I) and the biochemical characterization of one of its gene products. As a member of the Muscular Dystrophy Association's Scientific Advisory Committee, Henry was a prime mover in the formation of the Task Force on Genetics that sparked the successful resolution of the molecular genetics of Duchenne muscular dystrophy. While at Baylor College of Medicine, Henry was co-director of the Jerry Lewis Neuromuscular Disease Research Center.

When Henry became chair of the Department of Neuroscience and Cell Biology at UTMB, he was able to shape a department in his own vision. His leadership style was heavily influenced by his time at Stanford, and he borrowed the Arthur Kornberg approach to research, which stipulated that equipment and space should be accessible and shared by all. He particularly encouraged participation in what became known as the Friday lab meetings, where faculty and trainees from all over the university came to present their research-in-progress, grant proposals or recent papers of interest. It was a venue often feared by new trainees because of the level of rigor expected from any data presented. Although it was scheduled for a duration of two hours, it often went on

much longer, and it was common knowledge that no other meetings should be scheduled on Friday afternoon. Indeed, the intense discussions often took tangents ranging from scientific history to philosophy and revealed one of the most remarkable attributes of Henry: his ability to be conversant on almost any topic. Shortly before his death, Henry met with several faculty members at his house and noted that the Friday meetings were among the highlights of his career. These meetings continue after Henry's passing, and are a prominent legacy of his presence at UTMB.

During the latter part of his career, Henry's focus returned to protein folding, when his laboratory regained an interest in UNC-45. Henry's laboratory showed that the UNC-45 protein functions as a molecular chaperone to promote myosin folding and assembly into fully allosteric protein machines. UNC-45 proteins are now known to be nearly ubiquitous in fungi and animals, and dedicated isoforms are present for both skeletal and heart muscle myosins and for their cytoskeletal counterparts. Henry eventually became interested in the potential role of UNC-45 isoforms in mammalian heart development and disease, and also examined the potential role of these proteins in cancer development. UNC-45 research has blossomed into a small field comprising at least twelve laboratories around the world, where the structure/function relationships between UNC-45 and its myosin clients are being analyzed.

In his memory, the Henry F. Epstein symposium will take place during the summer of 2013 in Galveston, Texas, where some of Henry's trainees throughout the years will present scientific talks. Henry's many colleagues around the world and anyone with an interest in the various topics that Henry's career spanned are invited to attend. Henry will be sorely missed by his students, peers, friends and family. Our thoughts and condolences are with his wife Maxine and their children Adam and Daniel.

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