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Paul Sigler (1934–2000)

Paul Sigler (Fig. 1), one of the most influential of contemporary structural biologists, died suddenly of a heart attack on January 11, 2000. Paul was one of those rare individuals who shaped the development of structural biology not just by the example set by his own research career but also by the force of his personality. His unexpected death leaves a void that extends far beyond the boundaries of his own research interests. None of us worked closely with Paul, who was more senior to us, but we were influenced by him in different ways. By writing this obituary we hope to communicate to some degree the manner in which Paul Sigler engaged the hearts and minds of the scientists who were fortunate enough to encounter him.

Paul Sigler was born in Richmond, Virginia, on February 19, 1934. After his undergraduate studies in chemistry at Princeton University in 1955, Paul moved to Columbia University in 1959, where he obtained a medical degree. One thing that Paul appears to have been particularly proud of in his medical training was his championship status in delivering babies; he was pictured in a medical textbook demonstrating the proper way to hold a newborn infant after delivery. Despite this innate skill in midwifery, Paul felt the pull of structural biology, and he moved to the National Institutes of Health (NIH) in 1961, where he worked on chymotrypsin with David Davies. From 1964 to 1967 he was at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, UK, and he obtained a PhD in biochemistry from the University of Cambridge in 1967. He was appointed an Associate Professor of Biophysics at the University of Chicago in 1967, and was promoted to Professor in 1973. In 1989 he moved to the Department of Molecular Biophysics and Biochemistry, Yale University, where he was Henry Ford II Professor and an Investigator of the Howard Hughes Medical Institute.

Paul Sigler's trajectory through structural biology matches that of the field as a whole, moving from the early and painstaking investigations of individual protein structures to the present-day unveiling of the architecture and mechanics of large macromolecular assemblies. Paul's early work (with David Davies and David Blow) was mainly focused on crystallographic studies of chymotrypsin. Along with Brian Matthews, David Blow and Richard Henderson he published the structure of chymotrypsin and an analysis of its structural mechanism[1,2]. A paper on the iodination of tyrosine residues for the generation of crystallographic derivatives is still rewarding to read[3].

Paul subsequently worked on the structures of tRNA and phospholipases. He also developed an interest in transcription, working first on the structure of the bacterial trp repressor. The Sigler laboratory reported the structure of the trp repressor complexed to DNA in 1988, a structure that was instrumental in revising our view of the role of water molecules at protein–nucleic acid and protein–protein interfaces[4]. This structure was one of the first to be determined of a transcription factor recognizing a specific DNA target. Much to the surprise of all concerned, the structure revealed that a sheet of water molecules was interposed between the protein and the DNA. Paul Sigler suggested that the protein achieved specificity by 'reading out' the pattern of water molecules that are bound specifically to the DNA. This hypothesis met with considerable resistance because of the prevailing view that water molecules were too diffuse in structure to promote specificity. Paul was engaged, over several years, in a concerted attempt to resolve this controversy. He ultimately accumulated a considerable weight of evidence pointing towards the importance of water molecules in mediating specific interactions between proteins and nucleic acids and this is now widely recognized[5]. These water molecules are usually missing in structures of macromolecular assemblies determined at low resolution, and we think of Paul Sigler when we envision the waters that would be there but for the lack of resolution.

Figure 1
Paul Sigler, 1999. Photograph used, with permission, from Yale University.

After moving to Yale University, Paul became interested in cellular signal transduction, and his laboratory made contributions that are central to our current understanding of how heterotrimeric G proteins function[6]. Other work from Yale in this area includes the structural analysis of hormone-binding nuclear receptors. Perhaps most exciting among the recent results from the Sigler laboratory has been the elucidation of structures of the molecular chaperone GroEL–GroES[7]. These marvelous engines that drive protein folding are enormously intricate in their inner workings, and the crystal structures of various

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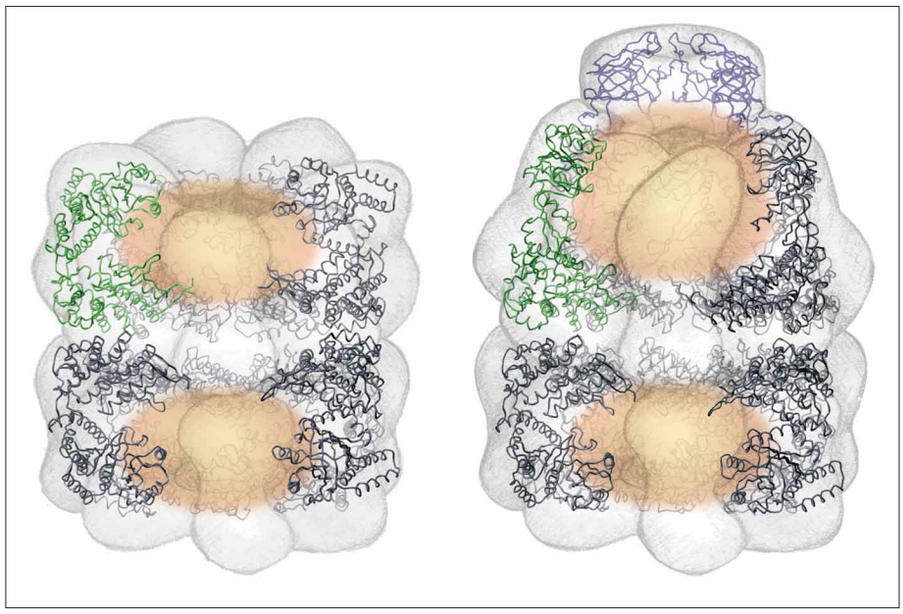

Figure 2

GroEL (left) and the GroEL–GroES complex (right), as determined crystallographically by the laboratories of Paul Sigler and Art Horwich at Yale. The assemblies are depicted as transparent molecular surfaces allowing visualization of the polypeptide backbone that comprises each structure. Each GroEL monomer is colored black, except for one, which is in green. GroES is colored in blue. The *cis*-folding chamber is represented as an orange surface. Used, with permission, from Lore Leighton.

states of GroEL–GroES that emerged from the Sigler laboratory, working in collaboration with Arthur Horwich and colleagues, were truly delightful to look at and tremendously fascinating to analyse mechanistically.

Paul Sigler had an enormous enthusiasm for probing into the mechanisms of protein machines, and in communicating what he had discovered to others interested in structural biology. His work with Horwich showed that the GroEL molecule functions as a 'two-stroke' engine that burns ATP molecules in order to cycle between two states in which the folding chambers dramatically rearrange their internal surfaces from ones that grab unfolded proteins to ones that let go[7]. When he first presented the structure of the GroEL–GroES complex at a Gordon Conference, he likened the symmetrical bullet-shaped structure, with its enlarged *cis*-folding chamber, to a temple. Indeed, the similarity is striking, and we can think of no better molecular structure to remember Paul by (Fig. 2).

Paul's energy and enthusiasm pervaded all of his interactions with colleagues in his Yale department and around the world. Unfettered by convention, Paul would often appear at faculty meetings and scientific conferences dressed in shorts and running shoes. At his departmental meetings Paul was always full of ideas about the direction of research, the graduate curriculum and the relationship of the department to the rest of Yale and the greater scientific community. At these conferences, as well as at national policy meetings, it was frequently Paul who, after listening patiently to a rambling discussion of an issue, would offer clear, insightful guidance that revealed his deep commitment to the interests of science. At departmental research seminars Paul would sometimes appear to be dozing in the front row, but he would rarely fail to raise a key question or to provide an important insight into a structural problem.

Graduate students, whether in his lab or not, were attracted to Paul for his wisdom, his disciplined thinking and, above all, his colorful personality. One part grandfather, one part stern parent and one part casual friend were stitched together into the bear-like personality that was Paul. His rich life experiences made him the source for guidance over such serious issues as scientific direction or career path, as well as an endless supply of fascinating stories and anecdotes, told usually with a gripping and dramatic flair uniquely his own. As a scientific superior, he was tough and demanding yet fair and, above all, encouraging. Whether lecturing to large audiences or in a one-on-one conversation, he had the unusual ability to make the difficult to understand seem easy. He never strayed from his chosen 'profession' of solving problems and then telling how he did it, usually with an unforgettable half-smile on his face.

Paul's presence livened up many casual social gatherings such as the departmental retreats or Friday afternoon 'happy hours'. At these gatherings, Paul was eminently approachable and would eagerly discuss the latest scientific results (his or yours), as well as the state of his favorite sports teams. Paul was a frequent character in the show, performed by second-year graduate students at the annual holiday party, that spoofed the faculty. He thoroughly enjoyed his portrayal in these shows knowing full well that imitation is the sincerest form of flattery.

In all of Paul's endeavors his absolute passion for science and for his partners in science was an overriding theme. We miss him, and as structural biology continues to unfold the workings of the cell at the molecular level, we regret that Paul will not be here to share our delight in the wonders to come.

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DAVID JERUZALMI AND JOHN KURIYAN

Laboratories of Molecular Biophysics, Howard Hughes Medical Institute, The Rockefeller University, New York, NY, USA.

JENNIFER DOUDNA

Dept of Molecular Biophysics and Biochemistry, Howard Hughes Medical Institute, Yale University, New Haven, Connecticut, USA.