

## Obituary: Paul Sigler

### David R Davies

Address: Laboratory of Molecular Biology, NIDDK, NIH, Bethesda, MD 20892-0560, USA.

E-mail: David.Davies@nih.gov

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The structural biology community was shocked and saddened to learn of the sudden, untimely death of Paul Sigler on January 11th. Paul was the Henry Ford II Professor of Biophysics and Molecular Biology and Howard Hughes Senior Investigator at Yale University and was a crystallographer of international renown. Born in Richmond, Virginia, he graduated from Princeton *summa cum laude* in chemistry. He then went to medical school and continued with two years of residency at Columbia Presbyterian. Next, he made a major career change in coming to the National Institutes of Health (NIH) as a Research Associate.

I first met Paul Sigler in 1961. He was one of a wonderful group of MDs who came to the NIH under a program to introduce them to basic research in the sciences. We were recruiting for a new Laboratory of Molecular Biology that was being established under the auspices of Gordon Tomkins, and I welcomed the opportunity to discuss a possible research program with this large, formidable man. During the interview Paul was full of enthusiasm for his medical training and talked extensively about his clinical and diagnostic experiences. I pointed out to him that if he came to work with us he would probably never treat another patient, but his mind was made up and he joined our group.

Paul's powerful personality generated many entertaining stories. Some of these he himself enjoyed repeating and the following is an example from his early days at the NIH. Because he did not know any crystallography, he started with a project investigating strand-exchange in polynucleotide solutions, an experiment involving careful spectrophotometry. Paul was using a spectrophotometer belonging to our colleague Dan Bradley in the Mental Health Institute, and decided to hook up the sample to a water bath. Unfortunately, a hose connection broke and water flooded the optical chamber, thus effectively destroying the instrument. Then we moved to our new Laboratory in another building where our colleague Martin Gellert had a brand new state-of-the-art spectrophotometer that he allowed Paul to use. Paul again wanted to establish optimal conditions for his experiment and decided to flush out the sample chamber. He did this by blowing helium into the chamber and, as he watched, the slits



opened (a bad sign) and the signal dropped to zero. Much to our surprise, helium atoms were apparently able to penetrate the windows of the photomultipliers, destroying their ability to function. Paul never did understand why Marty refused to let him use the spectrophotometer again.

Undeterred by these initial setbacks, Paul turned to crystallography and got involved in the use of heavy-atom labeled inhibitors of  $\gamma$ -chymotrypsin. He and Viswanathau Sasisekharan also performed an important fiber diffraction study that contributed to the structural understanding of polynucleotides. This background in structural biology prepared him for his next postdoctoral period at Cambridge, where he, David Blow, Richard Henderson and Brian Matthews determined the structure of  $\alpha$ -chymotrypsin and also inspired his later interest in nucleic acids and DNA-binding proteins.

From Cambridge Paul went to Chicago where he developed a strong group of crystallographers and determined

structures for a number of proteins as well as a structure for fMet tRNA. Towards the end of his stay in Chicago he worked on the Trp repressor, leading to structures of the repressor complexed with DNA, a structure that highlighted the role of water molecules in complementary structures.

In 1989 he moved to Yale to become a Howard Hughes Senior Investigator. These last ten years could be described as the golden age of structural biology and Paul's accomplishments over this period made him without doubt one of the outstanding crystallographers in the world. He attracted a remarkably productive group of young scientists at Yale and demonstrated fine judgement in selecting interesting proteins for investigation. His many achievements led to major insights in several areas of research.

In transmembrane signaling he and his colleagues were leaders in the field; they determined structures for transducin and for a trimeric complex of G proteins. This work provided a basis for understanding the mechanisms of GTP-induced release and activation of the  $G\beta\gamma$  complex. In transcriptional regulation the structures of repressors, receptors and transcription factors, all interacting with the appropriate DNA, provided a uniquely broad view of some of the major players involved in the assembly of a transcription complex. In the field of protein folding the determination of the structure of the chaperonin GroEL was truly spectacular, revealing a large, porous sevenfold symmetric cylindrical structure. Together with their subsequent structure of the GroEL–GroES complex this work provides a basis for understanding the mechanism by which these large assemblies assist in protein folding. Any one of these results would be an excellent contribution to structural biochemistry, to have accomplished all three was outstanding.

Working with Paul was exciting. He had a passion for doing the best experiments and a very low barrier to trying new methods. He was broadly read with a strong background in chemistry. He could be highly competitive and driven, but was also warm and discursive. He loved to discuss new ideas and results and his enthusiasm was contagious.

He will be greatly missed by his family, friends and colleagues. His work was spectacular and there was no indication that it had reached its peak. His untimely passing is a major loss to structural biology.