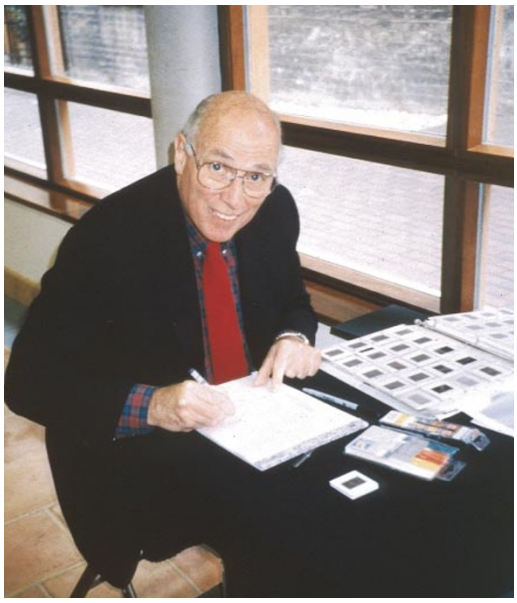
Paul Sigler: A structural biologist with passion

Richard Henderson

Paul Sigler had a passion for life and a passion for science. He was a wonderful character who was strongly supportive of everyone he worked with and deeply committed to scientific research. He died on the morning of January 11 after a sudden cardiac arrest while walking to work at Yale.



1934–2000

Paul was born in Richmond, Virginia, raised in Buffalo and graduated *summa cum laude* from Princeton in Chemistry in 1955. He trained in medicine at Columbia University receiving an M.D. in 1959, and completed his internship and residency at Columbia-Presbyterian Medical Center. Attracted by the intellectual excitement of structural biology in the early 1960s, at just the time that the atomic structure of myoglobin and the quaternary structure of hemoglobin were being unveiled, Paul walked into the office of David Davies at the National Institutes of Health in Bethesda and said he would like to learn protein crystallography.

With David Davies, he worked on the structure of the proteolytic enzyme γ-chymotrypsin[1] developing the first rational, active site heavy atom derivative by reacting the enzyme with para-iodophenylsulphonyl fluoride. With its isomorphous partner toluene-sulphonyl-fluoride, the pair produced an exceptionally isomorphous single site iodine derivative which subsequently helped to solve the structures of α-chymotrypsin, γ-chymotrypsin and elastase.

He then joined David Blow and Brian Matthews at the MRC Laboratory of Molecular Biology in Cambridge in 1964 where he spent three years working in an exceptionally productive collaboration that resulted, toward the middle of Paul's third year, in the structure of α-chymotrypsin[2]. Paul also took the opportunity to obtain a Cambridge Ph.D. — at the mature age of 30 he was David Blow's first graduate student. This was an exciting time for Paul since the chymotrypsin structure was only the third or fourth protein structure to be determined. After myoglobin and lysozyme, the structures of the enzymes carboxypeptidase and ribonuclease both came out at about the same time as α-chymotrypsin in early 1967. As a young Ph.D. student who had just joined the group, I remember the celebratory party where, after consumption of much wine, Paul and Brian Hartley wondered whether the true secrets of life had been revealed to them or whether it was simply a case of *in vino veritas*. He often played a prominent part in laboratory social activities where his imposing presence (Fig. 1) would dominate.

During his last year in Cambridge, Paul was already spending part of his time planning imaginative, ambitious projects for the future and designing his new labs in Chicago where he moved in 1967. As always, his enthusiasm then focused on his new life in Chicago. He was a powerful advocate of local city schools in downtown Chicago which his children attended, an enthusiast for the region which extended to taking visitors for morning and evening swims in Lake Michigan, and most of all ambitious for the success of protein crystallography in the Biophysics Department at the University of Chicago. Protein crystallography in the 1970s was already a powerful method, but the techniques that revolutionized the method in the 1980s — namely cloning and overexpression, area detectors, synchrotron sources and especially the freezing of crystals at liquid nitrogen temperature — had not yet been established. Paul's group made progress in those more difficult days with structures for the methionine initiator tRNA[3], phospholipase A_2 (ref. 4), and TrpR[5], the tryptophan repressor from *E. coli*. The impact of the first two of these structures was partially eclipsed by the earlier higher resolution analyses of yeast phenylalanine tRNA and by earlier phospholipase structures by other groups. However, with the TrpR structures in complexes with ligand and DNA, Paul's group finally had a substantial impact and this brought with it an invitation to join the Yale Structural Biology community, which was bigger and better resourced than that in Chicago. With support from the Howard Hughes Medical Institute, it was at Yale that Paul and his growing group became a major force in structural biology. His work flourished, he was able to expand it to tackle many of the most interesting problems in biology, and with the Yale environment of students, postdoctoral fellows and like-minded faculty colleagues, Paul's group made extraordinarily rapid progress in three major areas.

His work on protein–DNA interactions was extended to the yeast PolII TATA-box binding protein and its complex with DNA and transcription factor IIA, which revealed how these proteins bent and unwound the DNA for the initiation of transcription[6]. Work on the DNA binding domain of the glucocorticoid receptor[7] showed another example of DNA sequence recognition by a protein.

His work on the transducin complexes that are central to the mechanism of visual signal transduction in the retina began with a superb analysis of the structure of Tα[8], followed a year or two later by structures for the Tβγ dimer[9], the complex of dimer with the phosphodiesterase inhibitory subunit, phosducin[10] and the full Tαβγ trimer[11].

This work, begun in collaboration with Heidi Hamm in Chicago, had moved with him to Yale, where talented colleagues were able to translate Paul's ambitious ideas into hard structures. The mechanisms of signal transduction revealed by these structures, paralleled by related work at the University of Texas Southwestern Medical Center in Dallas, lie at the heart of vision, smell and taste as well as mediating the action of many neurotransmitters and hormones in human physiology.

Recently, Paul and his Yale colleagues determined the structure of the bacterial chaperonin GroEL[12] and the GroEL–GroES complex[13] in several conformations. This work showed that the molecules form a large symmetrical double-ring structure with two chambers that, driven by ATP hydrolysis, act alternately to provide a hydrophobic and a hydrophilic environment, helping to force a cycle of repeated attempts to fold certain cellular proteins that are reluctant to fold up spontaneously into their correct three-dimensional structures. In addition to these major achievements, Paul and his group carried out a host of other crystallographic structure determinations, ranging from work on transcription factors to studies of domains of other proteins involved in cellular regulation. This made his group one of the most productive structure groups in the world. In 1992, he was elected to the National Academy of Sciences (USA). He was about to lecture and receive the Sir Hans Krebs Medal at the Federation of European Biochemical Societies (FEBS) meeting in a few months.

Paul was a charming and engaging colleague with a delightfully critical and self-deprecating sense of humor. He was extraordinarily ambitious, occasionally subject to apparently uncontrolled rages of frustration when some minor annoyance seemed to be preventing progress and enlightenment, but in reality he was a scientist and friend who was loved and admired by his many colleagues. At a meeting in 1997 to mark the 30th anniversary of the α-chymotrypsin structure, Paul's talk focused on his most recent work but also included his view of the evolution of the universe (of protein crystallography). It consisted of six landmarks in the B.C. era (before chymotrypsin) — the big bang, the DNA double helix, Blow and Crick on phasing, myoglobin, the rotation function (including minor setbacks when Michael Rossmann began to write computer programs and introduced the concept of the fifth quadrant), and lysozyme. He described his disappointment in the early days when he was learning computing. The results of the previous day's computing would provide Brian Matthews and Bob Diamond with large piles of paper, but there would be only one page for Paul because a comma or bracket was missing. Fortunately, as the requirements for computing became more forgiving and the physics of data collection became more automated, Paul's skills and imagination in chemistry, biochemistry and molecular biology came into their own and allowed him to tackle the enormous range of structural studies that have produced such prolific results in the last few years. At Yale, Paul created a laboratory from which a continuing stream of outstanding structures flowed. At the age of 65, he had just renewed his appointment as an HHMI Principal Investigator, and had been looking forward to another seven years of exciting science. During his career he published well over a hundred articles reporting his research results.

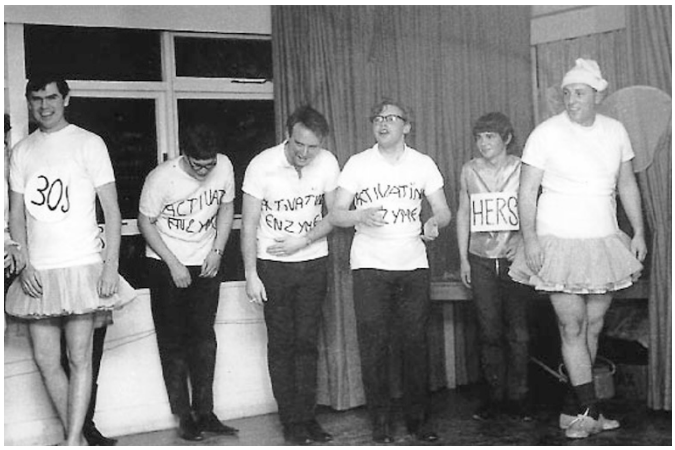


Fig. 1 Paul Sigler (far right) appearing in a laboratory Christmas pantomime sketch at the MRC Laboratory of Molecular Biology in Cambridge, in 1967. He is starring as 'magic magnesium'. The others in the photo of the 'ballet of protein synthesis' are, from the left: Steve Martin (just out of the picture), John Abelson as the 30S ribosomal subunit, Robin Buckland, David Shotton, Graham Jones, and a woman labeled HERS whose identity is not known.

Earlier in his career, Paul had been a Fellow of the Helen Hay Whitney Foundation, which has supported many outstanding young scientists since its postdoctoral fellowship program began in 1956. Paul was delighted to take over from Maclyn McCarty as Chair of the Foundation's Scientific Advisory Committee a few years ago (McCarty had been the Chair since the time Paul was a fellow 30 years earlier). Paul had just the right, larger than life character to oversee the Foundation's activities, and he took great pleasure doing so.

Paul is survived by his wife Jo, whom he married 41 years ago. They brought up five children who are now living in England, Israel, California, New York and Illinois. Our sympathy goes to them all and to past and present members of his group.

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