Obituary

Paul Sigler (1934–2000)

Paul Sigler died of a heart attack on 11 January. Once met, he was a man whom it was impossible to forget. His zest for science and for life was unmatched.

I was a freshly minted PhD working with David Blow at the MRC Laboratory of Molecular Biology, Cambridge, UK, when in 1964 Sigler joined the group as a PhD student. He was physically imposing, loud, opinionated and always in a rush. One of his first acts was to break off the tips of the glass pipettes so that the liquid would run out more quickly and he could complete his experiments faster. In many ways he qualified as the prototypical Ugly American. In fact, he engendered only warmth and affection. He was smart, a born raconteur and, above all, had unbounded enthusiasm.

Sigler was an undergraduate at Princeton University, trained as a physician at Columbia University in New York, and completed his internship and residency at Columbia-Presbyterian Medical Center. For reasons that are unknown, at least to me, he decided to forgo a career in medicine for one in structural biology. In 1961 he walked into the office of David Davies at the US National Institutes of Health (NIH), introduced himself, and said that he wanted to learn protein crystallography. In Davies' laboratory he showed that pipsyl-fluoride could be used both to locate the active site of the enzyme γ-chymotrypsin and to introduce a heavy atom (iodine) which might be used to help determine the enzyme's three-dimensional structure.

A Sigler characteristic was his view that it should be possible to reproduce, then improve, any procedure or result described in the literature. His experimental dexterity, however, did not always match his goals. Sigler himself would recall with relish how, at NIH, he decommissioned two spectrophotometers in succession — the first when, in attempting to control the temperature of the sample, he flooded the optical components with water; the second because, in trying to reduce absorption, he introduced helium, which penetrated into and ruined the photocell.

From the early involvement with γ-chymotrypsin, it was a natural transition to join David Blow, who was working on the structure of its sister enzyme α-chymotrypsin. The timing was impeccable. Before Sigler's arrival, the structure of only a single protein (myoglobin) was known at atomic resolution. Shortly thereafter, in 1965,

Enthusiasm and achievement in structural biology

David Phillips' group in London determined the structure of the second (lysozyme). By the time Sigler left Cambridge he had not only played a key part in the structure determination of α-chymotrypsin, but had also witnessed parallel determinations of two further proteins, ribonuclease and carboxypeptidase. Structural biology had arrived.

After the heady success with α-chymotrypsin, Sigler's move in 1968 to an independent position at the University of Chicago was followed by testing times. He was always attracted to those problems of the greatest biological interest and chose to invest the resources of his laboratory in an assault on the structure of methionyl transfer RNA. It had the promise of a spectacular accomplishment — the first determination of the three-dimensional structure of any RNA molecule. In the event, the groups of Alex Rich at the Massachusetts Institute of Technology and Aaron Klug at the Medical Research Council had superior crystals of the related phenylalanine transfer RNA and reached the goal first. Also, Sigler's determination at Chicago of the structure of trp repressor in complex with DNA was controversial because it lacked direct contacts between the protein and the DNA. As it turned out, however, the work proved to be highly valuable in emphasizing the function of water in mediating protein–DNA interactions.

It was at Yale University, to which he moved in 1989, that Sigler was to have his greatest impact. Support provided by the Howard Hughes Medical Institute, and the infrastructure and environment provided by the Yale structural biology group, allowed him to pursue some of the most enticing problems in biology and led to an extraordinary series of accomplishments.

First, he was able to determine the structure of the protein–DNA complex that is the heart of the machinery that regulates gene expression in all higher organisms. His work, together with that of Stephen Burley at the Rockefeller University, showed for the first time how formation of the complex causes the DNA to be severely bent and unwound. This unprecedented deformation of the DNA underlies the assembly of the overall complex. Related studies also showed how small molecules such as steroid hormones can turn genes on or off.

Second, he showed how a cell can transmit external signals to modulate activities within it. This work centred, in particular, on the way in which light is sensed by the eye. Sigler's determination of the structure of transducin, together with parallel studies of a related protein by Stephen Sprang and Alfred Gilman at the University of Texas Southwestern Medical Center, showed how so-called G proteins mediate signal transduction. This mechanism operates not only in vision but in many biological processes, including smell and the action of stimulants such as adrenaline.

Finally, in a technological *tour de force*, Sigler and his group determined the three-dimensional structure of the bacterial chaperonin GroEL/GroES, a large double-ring structure that forms two back-to-back compartments. Within these chambers, proteins that are being folded to their active shapes can be protected from the crowded environment of the cell. Knowledge of this structure made it possible to see, for the first time, how the process might work (in Sigler's words) "like a two-stroke motor".

At the same time, Sigler could always be relied upon to enliven any meeting or discussion. His large, witty, inquisitive presence invariably left a lasting impression. This is the Paul Sigler we shall remember: demanding yet self-deprecating, competitive yet appreciative of the work of others, a seeker of the big picture yet keen to discuss the results of his most junior colleagues. **Brian W. Matthews**

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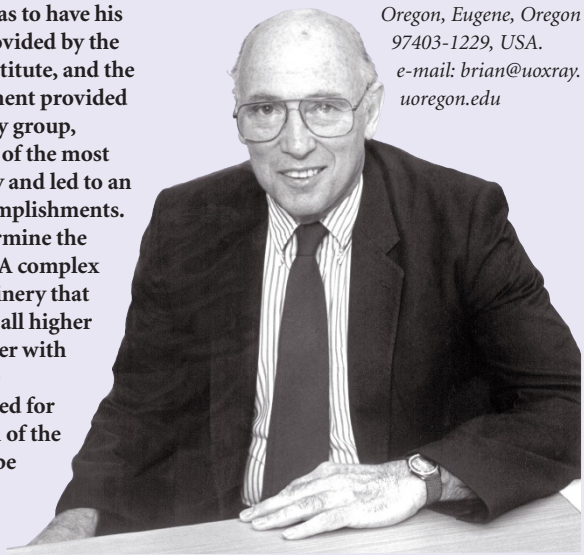

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