Obituary

David Phillips (1924–99)

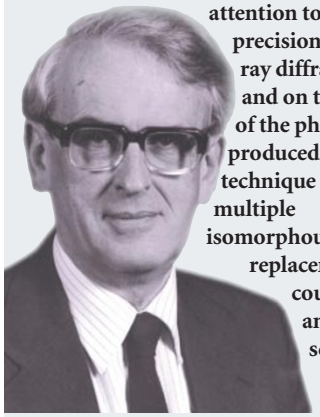
A founding father of structural biology

Nineteen sixty was the spring of hope for protein crystallography. The determination of the structures of myoglobin at 2-Å resolution by John Kendrew and of haemoglobin at 5.5 Å by Max Perutz had shown how structural studies could yield biological information. Yet, for several years, no new protein structures were solved and anxiety set in. Maybe the globins had been flukes.

David Phillips's structure determination of lysozyme in 1965 completely changed that view. This work first showed the power of protein crystallography to explain biological function in terms of physics and chemistry. It changed forever the way that enzymes are studied and was the start of the explosion in the number of protein structures being solved.

Following a war-time undergraduate degree in physics, mathematics and electrical engineering at Cardiff University, and subsequent appointments in Cardiff and Canada, Phillips took a post-doctoral position at the Royal Institution, London, in 1956. Sir Lawrence Bragg was director and fostered a spirit of independence and initiative there. Realizing that automating the collection of X-ray diffraction data was a prime objective for studies of large protein molecules, one of Phillips's first tasks was to collaborate in the design and construction of an automated diffractometer, an analogue device based on a mechanical model of the diffraction lattice. With this instrument he and his team were able to obtain highly accurate data which, in turn, led to precise structures (including that of myoglobin at 1.4-Å resolution, an astonishing precision for that era).

The solution of the X-ray structure of lysozyme was based on meticulous attention to the precision of the X-ray diffraction data and on the quality of the phases produced by the technique of multiple isomorphous replacement coupled with anomalous scattering measurements. The structure showed the complete path of the polypeptide chain (129 amino-acid residues) folded into both α-helices, as seen in myoglobin, and β-sheet, a structure that had been predicted by Linus Pauling but not hitherto observed in three dimensions.



GODFREY ARGENT

Lysozyme has antibacterial activity, which was then known to be due to its ability to hydrolyse the polysaccharide component of the bacterial cell wall. Even in 1962 Phillips had been thinking about the catalytic mechanism, and suggested that, as a graduate project, one of us (Louise Johnson) should pursue binding studies on inhibitor molecules. By early 1966 these experiments had led to a detailed interpretation of lysozyme in complex with an inhibitor, tri-*N*-acetylchitotriose, and an understanding of the key elements by which lysozyme recognizes sugars. The next step was to work out precisely how lysozyme recognizes its hexasaccharide substrate in the bacterial cell wall. By molecular model building, and bringing all the available biochemical evidence to bear, Phillips produced a proposal for the way in which a substrate must bind — and, after further intense thought and insights from Charles Vernon, for lysozyme's catalytic mechanism.

Here was the first structural explanation of how an enzyme speeds up a chemical reaction. The proposals contained suggestions for essentially every structural contribution to the catalytic power of enzymes that has since been detected — proximity, ground-state distortion, alteration of catalytic-group pK_a by the unique environment of the enzyme, general acid–base catalysis, and transition-state stabilization by electrostatic and hydrogen-bonding interactions. The extrapolation from inhibitor binding to substrate binding was a remarkable feat of deductive reasoning. It was achieved in a mere three days — three days which Phillips described as the most rewarding he had ever spent.

In 1966, he was appointed professor of molecular biophysics at Oxford University, and fresh achievements followed. Most notably, with his graduate students he solved the structure of triose phosphate isomerase (TIM). This was the first example of an eight-fold α–β-barrel protein. David was too modest to call it a 'Phillips fold' but he took quiet pride whenever a new TIM-barrel (as it is now known) structure was announced. The number is now in the hundreds.

From about the mid-1970s Phillips began his second career, in science policy and administration. Scientific research, he believed, must be organized so that "Combined with the provision of the necessary infrastructure, it can release individual scientists to display their critically important gifts of spontaneity and originality". These were his goals when, from 1983 to 1993, he was chairman of the Advisory Board for the Research Councils (ABRC), the then intermediary body between government and the research councils.

His time at ABRC was not without controversy. On the one hand he had to deal with the demands for funding from scientists faced with the growth of scientific opportunities, the need for increasingly complex apparatus and facilities, and the growing importance of interdisciplinary research. On the other hand he fought to persuade government to deliver more money while recognizing the necessarily limited resources and pressures for concentrating them. He won the respect of both sides, emphasizing that only the best science should be funded, although some of his views on priorities were not generally appreciated at the time. The Member of Parliament Tam Dalyell has recounted that politicians were much in awe of him: one minister confided, "I read my brief three times before Phillips enters my office".

David Phillips was appointed a life peer in 1994. He chose to keep his surname for the title ("Otherwise one disappears behind a different name and nobody quite knows who you are"); but, because there had been a Lord Phillips before, he became Lord Phillips of Ellesmere, after his birthplace, a small town in Shropshire close to the Welsh border.

Even when cancer had him deep in its grip, David remained at work and he completed a manuscript, "How the lysozyme molecule was actually solved", just nine days before his death on 23 February of this year. As Conan Doyle has Watson say in *The Final Problem*: "This was one of the best and wisest men we shall ever know". He was a man of remarkable warmth and sensitivity — a true friend in the best sense of the word.

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