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OBITUARY

David Chilton Phillips, Lord Phillips of Ellesmere KBE, FRS (1924–1999)

David Phillips was an outstanding scientist, one of the founding fathers of structural biology and a wise and influential figure in science and government. He started his research career with work on X-ray intensity statistics, then moved to small molecule crystallography, followed by protein crystallography and instrument design. Protein crystallography led to proposals for structure/function relationships, homology modeling, fundamental understanding of thermal motion, and several new protein structures of pharmaceutical interest. However, it is for his work with lysozyme that he will be most widely remembered. In 1966, he and the team, working at the Royal Institution in London, solved the first structure of an enzyme, lysozyme: from the structure it was immediately possible to put forward proposals for catalytic activity. The work first showed the power of protein crystallography to explain biological function in terms of physics and chemistry. It opened the way to the explosion in the number of protein structures that are now being determined with modern technology, and for the insights that these structures provide for the benefit of fundamental research, medicine, and agriculture.

David was awarded a first class wartime degree in Physics, Mathematics and Electrical Communications (1942–1944; 1947–1948) at University College Cardiff. The degree course was interrupted (1944–1947) for service in the RNVR as a radar officer on HMS *Illustrious*, a fleet aircraft carrier. He remained at Cardiff for his Ph.D. and began work in crystallography under the supervision of A.J.C. Wilson, the instigator of the "Wilson" plot of the probability distribution of X-ray intensities. He made contributions to intensity probabilities, the reliability index, and solved the structures of ephedrine hydrochloride, a component of antidecongestant nasal drops, and acridine. After a post doctoral period at the National Research Laboratories, Ottawa (1951–1955), David was attracted home in 1956 to the Royal Institution of Great Britain in London by Sir Lawrence Bragg.

Bragg had recently retired from the Professorship of Physics at the Cavendish Laboratory Cambridge. There he had presided over the fundamental studies by John Kendrew on myoglobin and Max Perutz on hemoglobin, the first protein crystal structures to be solved by X-ray diffraction methods. Bragg was keen to set up a protein crystallography laboratory in London. Among those whom he attracted, in addition to David, were Colin Blake, Tony North, and Roberto Poljak, who came in late 1960 from the United States bringing crystals of lysozyme. Realizing that automating the collection of diffraction data was a prime objective for studies of large protein molecules, one of David's first tasks was to join Uli Arndt in the design and construction of an automated diffractometer. This instrument, adapted to make multiple simultaneous measurements

David Chilton Phillips (Photo taken by M.N.G. James at Lake Obed, near Edmonton in 1990)

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of intensities, was to have profound consequences. With the linear diffractometer, David and his team were able to achieve data of high precision that in turn led to precise structures. David participated in the latter stages of the work on myoglobin. In 1961, the linear diffractometer was used to extend the data of the myoglobin crystals to 1.4 Å resolution, a remarkable precision in those days.

Work on lysozyme started seriously in 1961, a time that David described as the spring of hope. The work proceeded with intense care in the measurement of intensities, their corrections for absorption, the preparation of heavy atom isomorphous derivatives, and use of anomalous scattering. The solution of the 2 Å resolution structure of lysozyme was achieved in 1965, a time for a dual celebration with Bragg's 75th birthday. The map was spectacularly clear. Knowledge of the amino acid sequence, determined independently by Canfield and by Jolles, allowed a swift and definitive interpretation. The structure showed the complete path of thepolypeptide chain (129 amino acid residues) folded into both α-helices, which had previously been recognized in myoglobin, and β-sheet, a structure that had been predicted by Linus Pauling but not hitherto observed in three dimensions. The molecule was composed of two domains. Low-resolution (6 Å) inhibitor binding studies, which had begun in 1964 by myself as a graduate student working with David, showed that the catalytic site was located between these two domains.

The inhibitor binding studies were extended to 2 Å resolution by early 1966. Data collection was laborious; a data set took 14 crystals and required nearly 3 weeks. The most informative result was obtained for the lysozyme-tri-N-acetylchitotriose complex. This led to a detailed interpretation of the lysozyme-inhibitor complex and the key elements of recognition at the catalytic site. The next step was to work out how lysozyme recognized its substrate, part of the polysaccharide component of the bacterial cell wall. It was known from the work of John Rupley that the trisaccharide was a very poor substrate, but that catalytic efficiency increased with chain length up to the hexasaccharide. By molecular model building and by a series of logical arguments that brought to bear all the available biochemical evidence including that on the specificity for bacterial cell wall substrates, with important contributions from Nathan Sharon, David was able to produce a proposal for the way in which a hexasaccharide substrate must bind. With Charles Vernon's insights into the nonenzymatic mechanisms of glycoside hydrolysis, it was possible to make proposals for the catalytic mechanism. This was the first time that structure had provided an explanation on how an enzyme speeded up a chemical reaction in terms of the structural constraints and physical chemical principles. The extrapolation from inhibitor binding to the substrate binding was a remarkable leap of deductive reasoning, achieved in 3 days. David described these 3 days as the most rewarding that he had ever spent. The mechanism was first presented at a Royal Society Discussion meeting held at the Royal Institution on February 3, 1966 and published in the Proceedings of the Royal Society in 1967. Subsequently, the proposed mechanism has been validated by a host of biochemical and structural experiments. For this work and his later achievements in protein crystallography, David was elected to the Royal Society in 1967 and as a Foreign Associate of the U.S. National Academy of Sciences in 1985. He was also awarded the Feldberg Prize, the CIBA Medal of the Biochemical Society, the Royal Medal of the Royal Society, the Charles Leopold Meyer Prize of the French Academy of Sciences, the Wolf prize, the Aminoff medal of the Royal Swedish Academy of Sciences, and many honorary doctorates and fellowships.

The work was rapidly appreciated in the United States and formed the focus of a National Academy of Sciences meeting held in 1966 and published in 1967. In the summer of 1966, David presented the lysozyme structure and mechanism at a Gordon Conference organized by Fred Richards and Chris Anfinsen. He used stereo slides for the first time in which the left and right images were presented on the screen simultaneously and filtered by the spectator wearing stereo glasses. Those arriving late after dinner, having enjoyed only a modest break around the New Hampshire drinking laws, were somewhat perplexed by the apparent double images.

In 1966, David was appointed Professor of Molecular Biophysics at Oxford University, a move funded by the Medical Research Council and promoted by Hans Krebs (then Professor of Biochemistry at Oxford), Dorothy Hodgkin, and John Pringle (then Professor of Zoology). The Laboratory became part of the Zoology Department where John Pringle had a vision of Zoology that ran all the way from molecular structures to populations. At Oxford there were new achievements in protein structures. In an article published in *Scientific American* (1966), David showed how knowledge of the lysozyme structure could predict possible folding pathways that the protein might adopt as it was being synthesized on the ribosome. In another first early example, David, Tony North, and Wyn Browne used homology modeling to show how a protein distantly related in amino acid sequence (α-lactalbumin) might adopt the same structure as lysozyme. The prediction was later verified by structural work from Ravi Acharya and David Stuart based on early crystallization studies of Rudolf Aschaffenburg and Roger Fenna. With Louise Johnson and Robert Tjian (an undergraduate visitor with Dan Koshland at Oxford) and others, the structure of a transition state analogue, a tetrasaccharide lactone, with lysozyme was solved. This work was published in 1974 and provided the first structural demonstration for the distortion of the sugar in site D. In 1979, with Peter Artymuik, Colin Blake, Michael Sternberg, and others the correlation of dynamic properties of lysozyme were reported, an early example that showed that temperature factors in proteins were more than simply fudge factors. With graduate students (Ann Bloomer, David Banner, Greg Petsko, and Ian Wilson), he solved the structure of glycolytic enzyme, triose phosphate isomerase. This was the first example of an eight-fold β-barrel protein, a fold that is now recognized as the most common fold. With another graduate student, Brian Sutton, the structure of the carbohydrate within the Fc fragment of immunoglobulin G was solved. He used to say that he felt like his scientific contributions in later years were as an enabler, allowing others to flourish. One of the happy outcomes of this role was the foundation of the Oxford Enzyme Group in 1969 with Rex Richards as Chairman, an association of scientists from many different departments at Oxford that met regularly (in the early years with a privately financed dinner) and promoted interdisciplinary research. The studies on triosephosphate isomerase that brought together Jeremy Knowles, Stephen Waley, and Robin Offord was one of the happy outcomes of the early work of the Oxford Enzyme Group.

From about the mid-1970s, David began his second career as an influential figure in the administration of science. From 1976–1983 he was Biological Secretary and Vice President of the Royal Society and during this time was instrumental in introducing the Royal Society University Research Fellowships, a scheme that has done much to promote the independent careers of gifted individuals. In his 1991 Bernal Lecture at Birkbeck College, David put forward his view that scientific research must be organized so that

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"combined with the provision of the necessary infrastructure, it can release individual scientists to display their critically important gifts of spontaneity and originality." He had a difficult time as Chairman (first part-time (1983–1990) and then full-time (1990–1993)) of the Advisory Board for the Research Councils (ABRC), the then intermediary body between government and the research councils set up to "advise the Secretary of State on the resource needs of the Research Councils, the Royal Society, and the Fellowship of Engineering." On the one hand, he needed to satisfy the increasing demands for funding from scientists faced with the continuing growth of scientific opportunities, the increasing need for more and more complex apparatus and facilities (often achievable only through international collaboration), the growing importance of interdisciplinary science, and the need for a variety of different organizations within which research can be conducted most effectively. On the other hand, he fought to persuade Government to deliver more money but recognizing the necessarily limited resources and pressures for concentration. Thus in 1987, the ABRC did not pull its punches in expressing acute disappointment that the Government's revised spending plans were insufficient either to avert a reduction in the volume of scientific activity or to allow for the necessary strategic reshaping of the science base in the United Kingdom. He put much stress on the importance of getting the balance right between various modes of funding, but saw no possibility of that if the total resources remained short of what was necessary. He won the respect of both sides, emphasizing that only the best science should be funded, although some of his views on choices, selectivity, and priorities were not generally accepted. His skills in committee were characterized by honesty, considerable oratory, and a gift for friendships. It is said that politicians were much in awe of him and were fearful of making some scientific mistake. Tam Dalyell, Labor Member of Parliament for Linlithgow, recounts that one Conservative Minister confided "I read my brief three times before Phillips enters my office."

David was made Knight Batchelor in 1979, Knight Commander, Order of the British Empire (KBE) in 1989, and appointed in 1994 to a Life Peerage as Baron Phillips of Ellesmere. As recounted to Max Blythe at the Oxford Centre for Twentieth Century Medical Biography, Oxford Brooks University, he chose to stay with his surname for the title ("otherwise one disappears behind a different name and nobody quite knows who you are") since there had been a Lord Phillips before he became Phillips of Ellesmere, after his birthplace, the small town in Shropshire close to the border with Wales. He sat on the cross benches in the House of Lords, although his views were left of center. His grandfather had been one of the first Trade Union Members for Parliament. He joined the House of Lords Select Committee on Science and Technology and became Chairman in 1997, contributing especially to a study of the information society and the needs of the United Kingdom and initiating important reviews, such as the Report on Resistance to Antibiotics. He presided over the most active session in the Committees history, producing in all nine reports.

In the last years of his life he was ill with cancer but took a keen scientific interest in the treatment that held the disease at bay for a considerable time. Just nine days before he died, he completed the final draft of a manuscript on "How the lysozyme molecule was actually solved" to be published in the new volume of *International Tables for Crystallography* (M.G. Rossmann and E. Arnold, eds.). It is a fitting tribute, assembled with historical accuracy and containing much that is instructive to modern day protein crystallographers. He once listed among his interests "talking to children." He had a simplicity and directness that was equally effective with children and with the most august members of his committees. Many have commented on his great wisdom and on how they had benefited from his guidance and support. He was a special person who moved from academic research to wider aspects of science policy and its implementation, with a drive to make an incisive contribution. He died in the early hours on February 23, 1999. He is much missed.

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