David C. Phillips

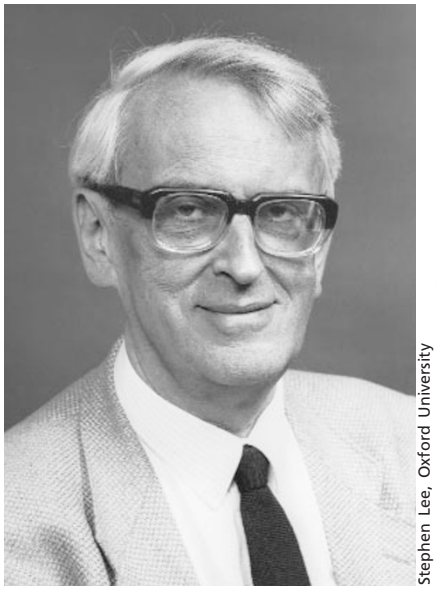
Anthony C.T. North

There were two major aspects to the scientific career of David Phillips. The first was his crystallographic research, most notably the role that he played in studies of lysozyme, the first enzyme to have its three-dimensional structure and mechanism determined by X-ray crystallography. This led to international recognition, with the consequent award of many prizes and medals, honorary doctorates and fellowships. The second was the part that he played in scientific organization both within the UK and internationally.

David was born in Ellesmere in Shropshire on the 7th of March, 1924; his father was a master tailor who was also a Methodist lay preacher. He attended Oswestry Boys High School and then studied physics at University College, Cardiff. After taking the reduced two-year degree course that had been mounted to provide graduates for wartime service, he became a radar officer on the aircraft carrier Illustrious, experiencing the dangers of carrying out experiments with high voltage equipment on the ship's metal deck.

After his naval service, he returned to Cardiff to work for a Ph.D. in the laboratory of A.J.C. Wilson. This led to the well-known paper describing a statistical method of distinguishing between centro-symmetric and non centro-symmetric crystals by their X-ray intensity distributions. He then went to the National Research Council laboratories in Ottawa for four years where he worked on the structures of organic molecules, including the carcinogen acridene.

In 1954, Sir Lawrence Bragg had taken up the appointment of Director of the Royal Institution. While in Cambridge, Bragg had encouraged the work of Max Perutz and John Kendrew, who were attempting to determine the three-dimensional structures of hemoglobin and myoglobin. Bragg needed to revitalize research at the Royal Institution and gained the support of the Medical Research Council to appoint a group of young workers who would collaborate with Perutz and Kendrew. Uli Arndt and Helen Scouloudi were already at the Royal Institution and were joined in late 1955 by David Phillips, David Green, Jack Dunitz and myself. David Phillips began by finishing off his acridene structure. Despite initial uncertainty as to whether to continue with small molecules or to embark upon protein structures, he decided to collaborate with Kendrew, taking charge of the 'London office' of the myoglobin project. The data for the myoglobin work were collected photographically on precession cameras and the films were scanned manually by use of a microdensitometer which produced traces of the photographic density along the lines of spots on the film. These traces had to be measured manually and several helpers were recruited to assist with this work. David Phillips, David Green and I traveled regularly to Cambridge in order to discuss the progress of the work and to use the EDSAC computer, one of the first two digital computers to be available in the UK. I recall one hilarious visit when we were discussing how to represent the three-dimensional electron density distribution in myoglobin in order to build a molecular model of the protein. It was decided to represent the density values by means of colored clips attached to steel rods. Our initial calculations showed that we would require about six miles of steel rods. This estimate was later lowered when it was realized that there would be no space for people to put their hands into the resulting forest. I was deputed to go to Hamley's toyshop in London, where I bought out their entire stock of Meccano clips. Such improvisation was a characteristic of the early days of protein crystallography!



Stephen Lee, Oxford University

1924–1999

David Phillips was keen to improve our methods of data collection and, jointly with Uli Arndt, whose life interest has been in instrument design, embarked upon building a 'linear diffractometer', a mechanical analog of the crystal reciprocal lattice. Equipped with a proportional counter, this device produced a direct printed output of the intensity of each diffraction spot and the intervening background. David's clear understanding of the principles of X-ray diffraction led to a later version of this machine with which three X-ray reflections were measured simultaneously with high precision, and punched out the results on paper tape which could be fed directly into a computer. In 1960, the structure of myoglobin was determined at high resolution and that of hemoglobin at a lower resolution, which nevertheless showed how the four myoglobin-like subunits were arranged. David, with Colin Blake who had now joined the Royal Institution team, then embarked upon a study of radiation damage to the myoglobin crystals.

In late 1960, Roberto Poljak also had come to the Royal Institution, having decided to take up protein crystallography, and he brought with him crystals of hen egg-white lysozyme. Lysozyme had been discovered by Fleming and it had been shown to have anti-bacterial activity, causing disruption of the bacterial cell wall. With the encouragement of Bragg and Phillips, Poljak embarked upon a systematic search for heavy atom derivatives. By October 1961, when I

returned from a year in the USA, progress appeared to be promising and a low resolution map of lysozyme was obtained in 1962. Unfortunately, unlike the low resolution maps of hemoglobin and myoglobin which had clearly shown rod-like features characteristic of α-helices, features of the lysozyme map were much less well defined; this was not entirely surprising as it was known that the proportion of helices in lysozyme was much smaller and that it contained four disulfide bridges linking parts of the chain together. Nevertheless, the result added to fears expressed in the USA by Joe Kraut that maps of proteins with low helical content might be uninterpretable.

The Royal Institution team was, however, undeterred and set out to improve instrumentation and computational methods and to obtain better heavy atom derivatives. At this stage, Roberto Poljak left London for Cambridge and, then, moved to the USA and David inherited the leadership of the lysozyme project. In those days, protein crystallography was very much a matter of teamwork, with the need to write computer programs from scratch, to design and build instruments for collecting data and to synthesize novel compounds for possible use for heavy atom derivatives. Spurred on by these challenges, the lysozyme team continued happily under the benign guidance of Sir Lawrence Bragg and in 1965 obtained a 2 Å resolution map of lysozyme from which an atomic model was built. The structure was determined in time for Sir Lawrence's 75th birthday party. The completed lysozyme model showed that the molecule did contain some α-helices and it also contained β-strands, with the four disulfide bridges linking parts of the chain together into a rather complicated fold[1].

Meanwhile, Louise Johnson had embarked upon a Ph.D. under David's supervision; she determined the structure of one of the bacterial cell wall saccharide components that had been shown to be a competitive inhibitor of the enzyme's activity and had therefore been thought to bind in the enzyme's active site. Low resolution studies of crystals into which this and related molecules had been diffused did indeed locate binding sites in a groove on the surface of the molecule. A high resolution map clearly showed the binding site for a trisaccharide molecule in half of the groove and, by model building, David showed that three additional saccharide units would fill the rest of the groove; one of the units had to be distorted slightly to fit into the groove and flanking the distorted unit were two acidic side chains. Just a few days later, a Royal Society discussion meeting was to be held at the Royal Institution on the subject of lysozyme and its activity. One of the speakers was to be Charles Vernon as an expert on enzyme mechanisms, and he visited the Royal Institution to discuss the structural work in preparation for giving his talk. He was able to identify the type of mechanism that would be consistent with the location of the features defined by the structural studies.

Three components were considered important in the mechanism — the two acidic groups on either side of the substrate and the distortion caused by fitting the substrate into the groove[2]. The role of the acidic groups was verified fairly soon by chemical modification, but the role of distortion remained a matter of controversy for some years. The inherent plasticity of protein molecules means that the enzyme itself could possibly be distorted in order to accommodate the undistorted substrate, but more recent structural studies by Strynadka and James[3] and by NMR have verified the presence of distortion in the bound substrate. All three features identified from the crystallographic studies have thus stood the test of time. They were well illustrated by the pictures by Irving Geis in David's much-cited article in Scientific American, November 1966, in which he also put forward a possible folding pathway for the protein.

Sir Lawrence Bragg was due to retire in 1966 and it was decided, with the promise of renewed support from the Medical Research Council, that the lysozyme group should move to the University of Oxford, to establish a new Laboratory of Molecular Biophysics with David as Professor. The move was not entirely welcomed by the Oxford establishment, some of whose members could not see the need for knowing the three-dimensional structure of biological molecules, but it was strongly supported by Sir Hans Krebs, John Pringle (the Professor of Zoology) and not least by Dorothy Hodgkin. Pringle's strong encouragement, coupled with the fact that his department was about to be given a new building, led to the Molecular Biophysics Laboratory being established rather surprisingly within the Department of Zoology.

Political fences were gradually mended and a very major step forward in collaboration was established through David's creation of the Oxford Enzyme Group with the enthusiastic participation of Rex Richards and Bob Williams, among others. This group brought together chemists, biochemists and biophysicists and set in motion powerful collaborations leading in the course of time to the formation of the Oxford Centre for Molecular Sciences.

After the move to Oxford, work continued on various aspects of the lysozyme project. These included the first example of protein modeling by homology, with the construction of a model of α-lactalbumin based on the close similarity of its amino-acid sequence to that of lysozyme. Other firsts in the early days of the Oxford laboratory included the use of the molecular replacement approach pioneered by Michael Rossmann and David Blow to solve the structure of the triclinic form of lysozyme, and the first use of computer graphics to interpret both the electron density maps of proteins and NMR spectra.

New projects soon arose, with David leading the determination of the structure of the enzyme triose phosphate isomerase (TIM), the first example of what has proved to be a very common protein chain fold (the TIM barrel). The laboratory in Oxford has continued to flourish, with the determination of many structures of proteins and viruses.

David was initially a slightly diffident lecturer, but he rapidly became a most proficient speaker with a precise and very clear style, perhaps inherited from his father. He gave the Royal Institution Christmas lectures in 1980 and of course many invited lectures at home and abroad. This led to a number of close friendships, for example with Fred Richards, who spent a sabbatical in Oxford during which he constructed the 'Richards optical comparator', a device to aid the construction of molecular models of proteins, which became known as 'Fred's folly' as it assumed alarmingly large proportions in the laboratory.

Soon after the determination of the lysozyme structure, David was elected a Fellow of the Royal Society and not long after he became a member of the Council of the Society. This began the second phase of his career. He served as Biological Secretary of the Royal Society from 1976 to 1983. This period was one of considerable difficulty for universities, with financial stringency all but halting the appointment of new younger staff. David was involved with the intro-

duction of the Royal Society Research Fellowship scheme which allowed the appointment of outstanding young scientists to positions in the universities.

For the 10 years from 1983 to 1993, David served as Chairman of the Advisory Board for the Research Councils (ABRC), a body set up to advise the government on the apportionment of funds between the several UK Research Councils, the Royal Society and the Fellowship of Engineering. Initially a part-time position, it became full time in 1989, when he returned to London from Oxford. This brought him into close contact with government and he found himself between the Scylla of Thatcherite funding restrictions and the Charybdis of the ever-increasing cost of scientific research. A particular difficulty was competition between the rapidly-increasing complexity of biological research, involving demands for advanced instrumentation, and the continuing need of physical scientists for expensive equipment. The advice of the ABRC to the government was normally made public and David was incensed when, in a particularly bad year for funding, the government refused to publish the advice they had received. He was apparently admonished for making known his criticism of this decision, but the following year did see a better settlement for the science budget.

The veteran Member of Parliament Tam Dalyell, who served for many years on the House of Commons Parliamentary and Scientific Committee, has recounted that politicians found David Phillips to be formidable, with a less than fully-informed opinion from them resulting in a "direct, glacial interrogative stare". Such a response was not unknown to his scientific colleagues and friends, though it quickly melted when a reasoned discussion ensued. I well knew that David's political views would not be exactly congruent with those of Margaret Thatcher, but he was as ever discrete when I asked how he got along with her, and merely recounted that when they were discussing possible applications of genetic modification of cattle, she responded "the meat would be tough". Dalyell considered Phillips to be "the most effective of all operators in that world where science meets politics", "making it abundantly clear that he considered it his duty to bring Members of Parliament face to face with reality" with his incisive, elegant, often provocative, but always pertinent contributions to discussion[4].

After his retirement from the ABRC, when it was disbanded, he was elevated to the House of Lords in 1994, where he took the title Lord Phillips of Ellesmere after his native town. In the current widespread discussion about the future of the House of Lords, it seems to me that insufficient heed is given to the role that highly experienced people such as David Phillips can contribute in that forum in guiding the direction of the country. He joined the House of Lords Select Committee on Science and Technology, and became its chairman in 1997, a post that he was forced to resign with great reluctance because of his increasing ill health. He contributed to debates on the role of women in science and to a very important study of the 'information society' which he was pleased to see was rapidly made available on the Internet.

David married Diana Hutchinson in 1960, and they had a daughter, Sarah; always fond of children, he took great delight in his two grandchildren. Diagnosed with prostate cancer 10 years ago, a succession of treatments kept the disease at bay and he was able to complete a lengthy historical account of "How the structure of lysozyme was actually determined" only 10 days before he died[5]. A highly talented scientist himself, a good listener with a prodigious memory and a great facility for friendship, he was a fine representative of UK science.

Anthony C.T. North is in the School of Biochemistry & Molecular Biology, University of Leeds, LEEDS LS2 9JT, UK. email: a.c.t.north@leeds.ac

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