

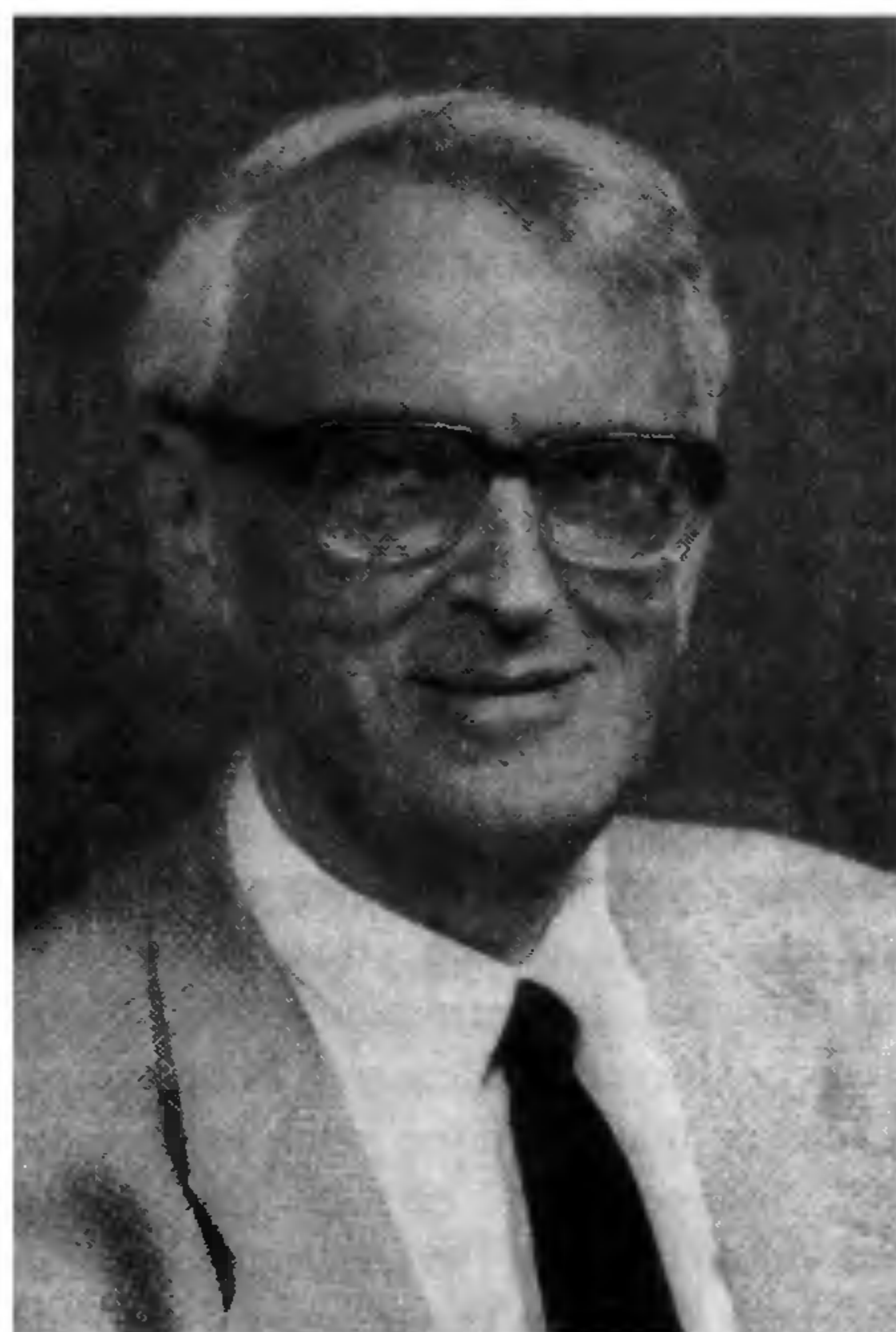
## Lord Phillips of Ellesmere KBE, FRS (1924–1999)\*

David Phillips was an outstanding scientist, one of the founding fathers of structural biology and a wise influential figure in science and government. He was Founder President of the British Crystallographic Association (1982–1984) and the spread of the Association's activities mirrored David's career in crystallography. He started with work on 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 modelling, fundamental understanding of thermal motion, and several protein molecules of pharmaceutical interest such as the immunoglobulin Fc fragment and  $\beta$ -lactamase. 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 opened the way to the explosion in the numbers 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 war-time 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 PhD and began work in crystallography under the supervision of A. J. C. Wilson, the instigator of the 'Wilson' plot of the probability distribution (as a function of  $\sin^2\phi/\lambda^2$ ) of X-ray intensities. He made contributions to intensity probabilities, the reliability index and solved the structures of ephedrine hydrochloride, a component of anti-decongestant 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 haemoglobin, 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 US bringing crystals of lysozyme. I joined the team in 1962. 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 of intensities, was to have profound consequences. With the linear diffractometer, David and his team were able to achieve data of high accuracy that in turn led to precise

structures. David had participated in the latter stages of work on myoglobin and 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. New data processing methods were developed by Tony North. 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, which was not yet published, allowed a swift and definitive interpretation. The structure showed the complete path of the polypeptide chain (129 amino acid residues) folded into both  $\alpha$  helices, that had previously been recognized in myoglobin, and  $\beta$  sheet, a structure that had been predicted by Linus Pauling but not hitherto observed in three-dimensions. The molecule was composed of 2 domains. Low-resolution (6 Å) inhibitor binding studies, that had begun in 1964, 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 that 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 evidences including that on

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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 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 of 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 three days. David described these three 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 3 February 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 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.

Following Bragg's retirement in 1966, David was appointed Professor of Molecular Biophysics in Oxford University, a move funded by the Medical Research Council and promoted by Hans Krebs (then Professor of Biochemistry in 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. In Oxford, there were new achievements in protein structures. In an article published in *Scientific American* (1966), Phillips 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 1979, with Peter Artymuik, Colin Bake and Michael Sternberg 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. In another first early example, he, Tony North and Wyn Browne used homology modelling to show how a protein distantly related in amino acid sequence ( $\alpha$ -lactalbumin) might adopt the same structure as lysozyme. 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 8-fold  $\alpha/\beta$  barrel protein, a fold that is now recognized as the most common fold. He used to say that he felt 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 1968, an association of scientists from many different Departments in Oxford that met regularly (in the early years with a privately financed dinner) and promoted interdisciplinary research. The Oxford Enzyme Group was the fore-runner of the present day Oxford Centre for Molecular Sciences.

David was elected to the Royal Society in 1967. From about the mid-70s he began his second career as an influential figure in the administration of science. From 1976–1983, he was Biological Secretary and Vice President at 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 '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 1983–1993 he was Chairman (first part-time and then full-time) 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'. He also served as member on the Advisory Council for Science and Technology (ACOST) and other Advi-

sory Councils. His skills in committee were characterized by honesty, considerable oratory and a gift for friendship. It is said that politicians were much in awe of him and were fearful of making some scientific mistake. He made a special plea for openness in the decision making process and in the decisions taken.

His time at ABRC was not without controversy. 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 the Government to deliver more money but recognizing the necessarily limited resources and pressures for concentration. 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. As recounted to Max Blythe at the Oxford Centre for Twentieth Century Medical Biography, he was once reprimanded by the Minister for making a public statement concerning his view of the poor treatment of the science budget in the annual government statement on Public Expenditure. The Minister conceded in private that the qualities required in a person in the advisory role on visionary uses of science resources would probably not be compatible with a person who would be willing to be snaffled and they came to a good understanding. The next year the Public Expenditure statement produced a much better settlement for science that recognized the need for a rising profile over future years.

David was made Knight Bachelor 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 (his birthplace). He sat on the cross benches in the House of Lords, although his views were left of centre. His grandfather had been one of the first trade union MPs. 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 UK and initiating important reviews, such as the Report on Resistance to Antibiotics.

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. He died in the early hours of 23 February

1999. Before he died, he completed the final draft of a manuscript on how the lysozyme molecule was solved. It is a fitting tribute, assembled with historical accuracy and vision 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 have benefited from his guidance and support. He was a special person who moved from academia to wider aspects of science policy, guided by a strong appreciation of history. He is much missed.

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## POSTDOCTORAL RESEARCH PROGRAMME IN BIOTECHNOLOGY & LIFE SCIENCES

Indian Institute of Science, Bangalore 560 012

(A programme sponsored by the Department of Biotechnology, Government of India)

Several Postdoctoral Research Associateships are available for bright young scientists to work in the frontier areas of modern biology at different departments of the Division of Biological Sciences of the Institute. The Associateship is purely temporary and is tenable for a maximum period of 2 years starting from 1 October 1999. The award is given initially for a period of one year and it is renewable for the second year on satisfactory performance.

Candidates holding Ph.D. degree in any branches of Life Sciences/Chemistry/Physics or MD and a uniformly good academic record are eligible for selection. Also candidates who have already submitted the Ph.D. degree thesis but awaiting the formal award of the degree are eligible to apply, but they will be appointed as Research Associates (Provisional) till they obtain the degree. Minimum consolidated emoluments for Postdoctoral Research Associates will vary from Rs 8400 to Rs 10400 per month. Single room accommodation will be provided in the hostel for the selected candidates.

Candidates may apply on plain paper with biodata, list of publications (include copies of reprints of important papers), copies of certificates (B.Sc., M.Sc. & Ph.D.), one-page synopsis of Ph.D. thesis, 2 letters of recommendation (academic) and a declaration by the candidate stating that if selected for the Associateship, he/she will complete 2-year tenure of the programme. **The interviews for the Associateships will be held at IISc, Bangalore, during mid-September 1999.**

Applications should be addressed to **Prof. K. Muniyappa, Department of Biochemistry, Indian Institute of Science, Bangalore 560 012**, before 20 August 1999, and should be clearly marked on the envelope as 'DBT Postdoctoral Associateship'.