OBITUARY

David Blow 1931–2004

Richard Henderson

David Blow died on 8 June 2004, aged 72. His career spanned 50 years of protein crystallography from his early student days, when ideas were the key, through the pioneering years when each new structure required enormous efforts but was wonderfully revealing when it emerged. By the time he became Emeritus Professor, X-ray diffraction from frozen crystals at powerful synchrotrons had transformed macromolecular crystallography into a superbly productive method. David's mathematical skills and his unique ability to organize the many developments needed on a broad front allowed him to contribute to the theory and practice of protein crystallography while simultaneously solving the structure of many important proteins and training many students and postdoctoral fellows.

Born in Birmingham, UK, in 1931, the second son of a Methodist minister, David had a somewhat nomadic education before attending Kingswood School, Bath, where he and his brother Ralph developed their interest in physics. Ralph went to Oxford and David won an open scholarship to Corpus Christi College, Cambridge, where after a delay for national service with the Royal Air Force (1949–1951), he read Natural Sciences.

In 1954, as a young physics graduate at the Cavendish Laboratory in Cambridge, he was looking for an exciting area of research when a friend told him about an Austrian scientist working there who was reputed to be good at getting money. This was Max Perutz. David went to see Max, was thrilled to hear about the work he was doing and immediately accepted the offer to become his student. Twenty years earlier, Max had himself been a student of Desmond Bernal and Lawrence Bragg, and by 1954 he was head of a small Medical Research Council (MRC) Unit for the Study of the Molecular Structure of Biological Systems with funds to support a research student. Max had learned from Bernal that the secret of life lay in the structure of proteins and that the only way to find the structure was by using X-ray crystallography. By the time David joined the unit in late 1954, there was still no sign of any protein structure and the opinion among many was that the task was hopeless. A few years earlier, Max himself had commented that attempting to analyze the structure of a protein seemed on the face of it about as promising as a journey to the moon. As it happened, the protein Max had chosen to study, on which David joined him, was hemoglobin, the oxygen carrier in the blood, whose atomic structure came out in 1968 just a year before a man landed on the moon. David therefore began his research career by learning to purify and crystallize horse, pig, dog and rabbit hemoglobin.

In 1953, Max had recognized that 'isomorphous replacement' might be able to solve the structures of protein crystals, having spent over 15 years trying many other approaches, each entirely plausible but ultimately unproductive. Isomorphous replacement consists of precisely attaching one or two heavy atoms to the protein to produce small changes in the intensities of the diffracted X-ray beams that can be used to deduce the phases of the Fourier components of the electron density. The key observation—that small intensity changes could be observed after the addition of the heavy atoms—had been made a year earlier (Green, D.M., Ingram, V.M. & Perutz, M.F. *Proc. Roy Soc. A* **225**, 287–307, 1954). Although this was an important start, there was still an enormous amount of detailed development to be done and it was this challenge that David found exciting.

David came up with a rigorous general method for deriving the phases and used it to determine a projection structure of horse hemoglobin. In this, he was helped by a discussion with Francis Crick, which led to the famous paper (Blow, D.M. & Crick, F.H.C. *Acta Crystallogr.* **12**, 794–802, 1959) on the treatment of errors in the isomorphous replacement method. David shared an office with Crick, who a year or two earlier with James Watson had proposed their model for the structure of DNA. By the end of David's Ph.D. in 1957, the first three-dimensional images of myoglobin had been obtained by John Kendrew and his colleagues, who were part of the same unit. The isomorphous replacement method has been used to solve the vast majority of new protein structures ever since.

David then spent two years as a Fulbright scholar at the National Institutes of Health and Massachusetts Institute of Technology in the United States with Alex Rich, working on deoxycholate fibers, where he learned it was better to work on crystals than fibers. By the time David returned to the MRC in 1959, the three-dimensional structure of myoglobin at atomic resolution and the 5.5 Å three-dimensional structure of hemoglobin had been worked out by the groups he had left behind in Cambridge. The papers were published in *Nature* in 1960, and Perutz and Kendrew were awarded the 1962 Nobel Prize for Chemistry, in the same year that Crick and Watson shared the Nobel Prize in Physiology or Medicine with Wilkins.

Toward the end of his American postdoctoral work, influenced by the missionary zeal of his Methodist parents and his older brother Ralph, David considered teaching in what is now Zimbabwe. However, surprised and delighted to be offered a post back at the MRC, he immediately agreed to return to Cambridge, and soon began a remarkable collaboration with another young scientist, Michael Rossmann, with whom he shared an office. Michael had arrived a year previously to work on hemoglobin, after two years in the United States working with Bill Lipscomb on terpenoids. They formed a tremendously effective and very positive working relationship. Michael said that, with his own Quaker education and David's Methodist upbringing, they had much in common. David said they got on so well because of their completely complementary personalities. Michael was tremendously enthusiastic and would go roaring off with lots of ideas. David would reflect, thinking about things more analytically.

During the next five years, they pioneered 'molecular replacement', the second major approach to solving protein crystal structures, developed in a classic series of papers in the early 1960s. Triggered initially by the finding that the structure of hemoglobin consisted of four subunits each very similar in structure to myoglobin, they thought that surely it should have been possible to determine the relationship

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between subunits directly from the diffraction patterns and that such knowledge might help to solve the structure. This led them to define the rotation function and the translation function, mathematical functions in Patterson space that could be used to find the relative orientations and positions of the subunits within the same or different crystal forms. They then suggested how knowledge of equivalent subunit densities could be used to generate or improve the phases. Nowadays, because so many protein structures are already known, molecular replacement can be used to solve a new structure very quickly by using existing knowledge of similar structures to bootstrap first to a rough and then to a refined solution.

Following the success of the work on hemoglobin and myoglobin, David decided to branch out and tackle a new protein structure. He chose chymotrypsin, a digestive enzyme from the gut. Brian Hartley, in the nearby Cambridge University Biochemistry Department, had been working on the mechanism and amino acid sequence of chymotrypsin, and had already tried to interest the crystallographers in it. Max, meanwhile, had persuaded MRC to build a new laboratory on the southern edge of the city to bring together the Cavendish Unit with another MRC-funded group led by Fred Sanger, and Sanger had recruited Hartley, also fresh from two years in the United States. As a result, David and Brian Hartley found themselves together in what became a long-term association, which began at the MRC Laboratory of Molecular Biology when it was opened by the Queen in early 1962.

On chymotrypsin, David first worked with Michael Rossmann using the rotation and translation functions to determine the arrangement of molecules in the monoclinic crystal form and to determine the structure at low resolution. Michael moved to Purdue University in 1964. David was joined first by Brian Matthews and then by Paul Sigler, forming an enthusiastic trio. By 1967, helped by several 'computors', young assistants who manually measured the intensities of diffraction spots on precession photographs, David's team had succeeded in determining the atomic structure of chymotrypsin. It was only the third or fourth protein structure to be determined. Thus, by age 36, David had helped develop the two methods that form the backbone of protein crystallography and had led the team that solved the structure of chymotrypsin.

With Brian Hartley and others, he went on to work out the mechanism of action of chymotrypsin, which was the first serine protease to have a fully understood structure and function and is a standard example in many biochemistry text books to this day. The structure of many other enzymes and enzyme complexes followed, initially in Cambridge and later at Imperial College of Science and Technology. Among these were the trypsin-soybean inhibitor complex, tyrosine-tRNA synthetase, glucose/xylose isomerase, cholesterol oxidase, carboxypeptidase G2 and collagenase. Some of the earliest crystal structures of enzymes with genetically engineered mutations were determined by David and his students at Imperial College. His group also developed new methods of protein crystallization, especially the microbatch method, in which tiny amounts of protein were crystallized in aqueous nanoliter droplets under oil. At Imperial College, David also encouraged young scientists to initiate their own projects and built the Biophysics Group into a significant force in structural biology.

In Cambridge and London, he had a strong commitment to teaching and trained many research students. This led him to take up first a teaching fellowship at Trinity College Cambridge in 1969, and then a professorship of biophysics at Imperial College in 1977—forming a cross-departmental alliance, unusual in universities at that time, with Brian Hartley, who had moved to Imperial College two years earlier as professor of biochemistry.

David's students and colleagues universally found him to be generous, modest, kind, fair, farsighted and persuasive. He was especially skillful at matching problems to people. Personally hardworking and thorough, he never sought credit for his own achievements, yet always ensured that his students and colleagues received proper recognition for theirs. These attributes meant he was in great demand first as Dean of the Royal College of Science at Imperial College (1981–1984) and, finally, as Head of the Physics Department (1991–1994).

He earned many scientific honors, being elected a Fellow of the Royal Society (1972) and Foreign Associate of the French Academy of Sciences in (1992), winning the CIBA medal of the Biochemical Society (1967), the Charles Léopold Meyer prize (1979) and the Wolf Prize for Chemistry (1987). The last two were awarded to David jointly with David Phillips ('the two Davids') for their respective work on the structure and function of chymotrypsin and lysozyme.

After retiring with a serious heart problem in 1994, David continued working part-time at Imperial College, writing and bringing projects he had started to a proper conclusion. His excellent book published recently, *Outline of Crystallography for Biologists*, displayed his long experience and many contributions to the field. During the last year, while coping courageously with lung cancer, he continued to write, producing a biographical memoir of Max Perutz (to be published by the Royal Society), a prehistory of the British Crystallographic Association that he helped to found in 1982, and even a short novel.

Many of his colleagues traveled to visit him in Appledore in North Devon, where in 1994 he had settled with his wife Mavis, returning to his roots in a village where his great-grandfather had lived three generations before and where he could enjoy walking and sailing. He and Mavis became enthusiastic members of the local community, Mavis as secretary and baritone horn player in the Appledore Brass Band and David as band roadie and architect of a Lottery grant to purchase new brass instruments, and as chairman of the local branch of the Campaign to Protect Rural England.

David married Mavis Sears in 1955, having met her while she was training as a French teacher at Homerton. He leaves two children, Elizabeth and Julian, and five grandchildren. He will be remembered by friends, colleagues and family as a gentle and kind man who always tried to encourage the best in everyone he met.

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