Professor Dorothy Hodgkin, OM, FRS

1910–1994

Professor Dorothy Hodgkin died at her home in Ilmington, Warwickshire, on Friday the 29th July, 1994. She was an outstanding scientist and a remarkable person. In 1964 she was awarded the Nobel prize for Chemistry for her work on the structures of natural products, notably penicillin and vitamin B_{12}, and during her life she received many other honours both for her scientific achievements, including her work on the diabetic hormone insulin, and her work for peace and understanding among different nations.

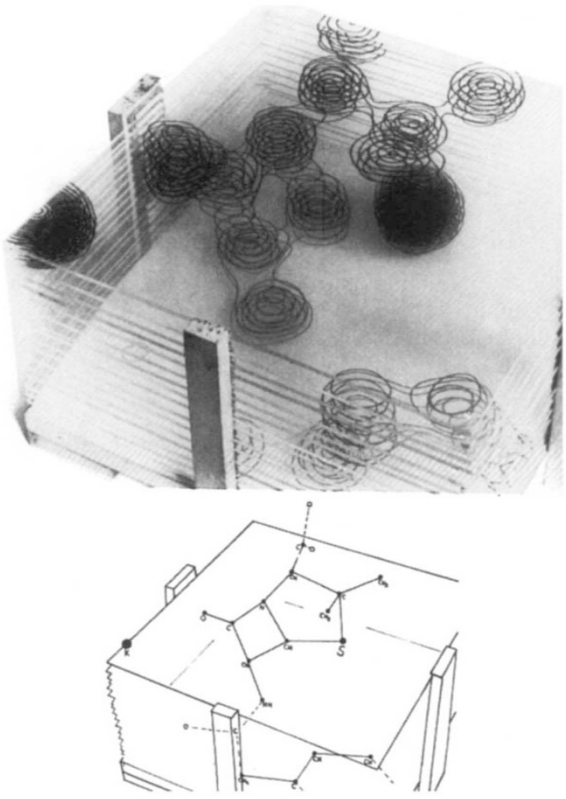
Dorothy's father, J.W. Crowfoot was Education Officer in Khartoum and both parents were archaeologists. Dorothy was born in Cairo and came to England at the start of the First World War. As a child Dorothy had become interested in crystals from growing them herself both at home and at school, and from reading W.H. Bragg's Christmas lectures "Concerning the Nature of Things". She came to Somerville College, Oxford in 1928 to read Chemistry and graduated in 1932 having done some practical studies on thallium alkyl halides, working in the Mineralogy Department with H.L. Bowman and H.M. Powell. The department was located in Ruskin's 'Cathedral of Science' — the University Science Museum in Oxford. Dorothy occupied part of a room where, at the British Association Meeting in 1861, there had been the famous debate on the origin of species between Bishop Wilberforce, Bishop of Oxford, and the scientist T.H. Huxley.

Dorothy continued her association with Somerville for the rest of her life except for a short time at Cambridge where she moved in 1932 to carry out her Ph.D. with J.D. Bernal, working on the structure of sterols before returning to Oxford, with a Fellowship at Somerville, two years later. She was Tutorial Fellow from 1935–55, Professorial Fellow from 1955–77, and Honourary Fellow from 1977 until her death. From 1960–1977 she was Wolfson Research Professor of the Royal Society.

In 1934 with J.D. Bernal she published the first paper describing X-ray diffraction from a protein crystal[1]. The crystals, which had been brought four weeks previously in the coat pocket of a visitor from Sweden, were shown to lose their crystallinity when exposed to air; Bernal and Hodgkin noted that this probably explained why previous attempts to obtain protein X-ray diffraction patterns had been unsuccessful. Their paper ends "At this stage such ideas [about the structures of proteins] are merely speculative but now that a crystalline protein has been made to give X-ray photographs, it is clear that we have the means of checking them and, by examining the structures of all crystalline proteins, arriving at far more detailed conclusions about protein structure than previous physical or chemical methods have been able to give". This prophecy is born out by the multitude of protein structures now being reported and whose structures determined by X-ray crystallography illuminate their biological function.

In the following year, Dorothy grew crystals of insulin from a microcrystalline suspension given to her by Sir Robert Robinson and in later accounts she described the thrill of seeing the regular array of tiny spots when she developed the first X-ray photograph. She was acutely worried that she may have lost the real insulin in the course of her operations. She carried out the checks herself to confirm that the crystals were in fact protein. She also sent the crystals to Henry Dale who measured their biological activity and found it to be 24 international units mg^{-1}; not very good, but good enough to establish the authentic character of the crystals. With these experiments the science of protein crystallography was born. In a letter dated 1936 Bernal indicated to Dorothy that cadmium insulin crystals existed and might be used for isomorphous replacement but it was not until 20 years later that Max Perutz established this method for the solution of protein crystal structures.

Penicillin had been discovered in 1929 by Fleming but he had not succeeded in isolating it so that it might be used for practical purposes. The isolation was achieved by Florey and Chain in Oxford in 1941 with the result that the antibiotic was available to treat casualties during the Normandy landings in 1944, and thereafter. Dorothy was drawn into this research in 1942 working first with crystals of the degradation products and then — in 1944 — with the sodium, potassium and rubidium salts of benzyl penicillin. The work involved close collaboration with the chemical investigations of E.P. Abraham, E. Chain, W. Baker and R. Robinson. Through comparison of the isomorphous potassium and rubidium salts and the sodium salt which crystallized in a different space group, the essential chemical structure of the molecule was established by the early summer of 1945. The conclusions reached were, in their final form, largely independent of any other evidence on the details of the molecular structure. The results, so confidently presented, were a triumph for the early days of natural product crystallography. The structure containing the seemingly unstable β-lactam ring fixed with a five membered thiazolidine ring was exceptional and drew amazement



Electron density map of penicillin over the thiazolide and β-lactam rings. The maps were drawn by hand onto transparent perpex sheets, section by section, and stacked to represent the three dimensional distribution (top figure). The molecular structure is shown below. (From Crowfoot, D., Bunn, C.W., Rogers-Low, B.W. and Turner-Jones, A. In Chemistry of penicillin (ed H.T. Clarke *et al.*) pp. 310– 366 (Princeton University Press, 1949).

from chemists. The work was of immense importance for understanding the antibiotic which was to have such revolutionary results in the treatment of disease. Her later work extended these studies to the structures of other penicillins and to cephalosporin.

Structural analysis in those days was not easy: intensity measurement of diffraction spots recorded with a Weissenberg camera were made visually (by a method which was still in use when I started in research in 1962); Bragg and Lipson charts were used to consider coordinates in a qualitative way in relation to intensities; Fourier calculations were carried out in projection with Beevers Lipson strips, although later punched card machines were used; and each structure was tested by the 'fly's eye' method of comparing the optical diffraction pattern of a mask representing the trial structure with the X-ray diffraction pattern. The optical diffraction studies of penicillin were carried out by C.W. Bunn at Imperial Chemical Industries, Northwich, in his spare time until Lord Melchett came round and saw papers marked 'penicillin' and expressed delight that ICI should be involved in the work. The project was then given a proper job number.

Pernicious anaemia, long thought to be incurable and usually fatal, had been shown in 1926 to be treatable by supplementing the diet with liver. The anti-pernicious anaemia factor, later called vitamin B_{12}, was isolated in crystalline form in 1948 and later that year small deep-red crystals were given to Dorothy. The formula of approximately half of the molecule was known from chemical studies (a nucleotide-like fragment, various amide groupings, and a large porphyrin-like nucleus containing cobalt) but the rest of the molecule and how the fragments were linked together were unknown. The structure, containing 93 non-hydrogen atoms, was solved in 1956 and represented the largest structure solved at that time. As in the work on penicillin, structure solution was achieved by the comparison of results with a number of different crystal forms and derivatives. By this time computer technology had advanced but it still took three weeks to calculate the final three-dimensional map.

Several features not previously observed in naturally occurring chemical structures were found. The most unusual of these was the existence of the cobalt-containing ring system, the corrin ring, which in A. Eschenmoser's words has been described as "perhaps the finest gift that X-ray analysis has so far bestowed on the organic chemistry of low molecular weight natural products". The corrin ring, like porphyrin, has four pyrrole units. Two are directly bonded to each other whereas the others are joined by methylene bridges as in porphyrins. The cobalt is co-ordinated by the nitrogens of the four pyrroles and by two other ligands. The novel bond from the cobalt atom to the C5' carbon of the deoxyadenosyl unit in the coenzyme B_{12} provided clues to the vitamin's biological function. The work gave new insights into chemistry as well as new methods for crystal structure solutions.

Insulin had first been crystallized by J.J. Abel in 1925 but difficulties were experienced later in repeating the crystallizations. These difficulties seemed to be associated with the introduction of glass vessels instead of metal buckets for the initial extraction. In 1934 D.A. Scott discovered that zinc, presumably leaching from the buckets, was an integral part of the rhombohedral crystals. He was led to this discovery by observing the occurrence of zinc in the pancreas. Dorothy first probed the structure of rhombohedral insulin crystals with X-rays in 1935 and showed that the unit cell contained three equivalent units of about 12,000 M_r. The size of the molecule was way beyond the size that could be tackled in those days. The basic repeating unit in the rhombohedral unit cell was later recognised to be two insulin molecules and their arrangement was detected by use of the rotational function in a joint paper of the Hodgkin group with Michael Rossmann in 1966. The dimers were arranged into a hexamer by operation of the crystallographic three fold axis.

The solution of the insulin structure was accomplished in 1969 by her team which included Guy Dodson, Tom Blundell, Margaret Adams, Eleanor Dodson, M. Vijayan, Marjorie Harding, B. Rimmer and S. Sheat. The structure determination was difficult. The spacegroup R3 had no centric projections which were important in those days for the detection and refinement of heavy atom positions. Solution of this difficulty was accomplished by the development of methods for incorporation of anomalous scattering data into the estimation of the protein-heavy atom structure factor amplitudes. The protein in the crystals was close packed and the protein contained no free sulphydryl groups and hence production of good heavy atom derivatives was difficult.

The breakthrough came when it was discovered that the zinc could be replaced by lead, although the crystals were non-isomorphous and did not immediately lead to a structure.

For insulin the crystallographic work was helped by knowledge of the chemical structure obtained by

Sanger in 1953. Once solved the structure of insulin provided definitive description of the arrangement of atoms. The resolution was extended to 1.5 Å and a very detailed account of both the protein's and its water's structure was published in 1988. Work on insulin has developed over the years — especially in Guy Dodson's laboratory in York — and has led to new insights, such as the recognition that in this instance the structure seen in the crystals is slightly different in conformation to that recognised by the insulin receptor, and to the ability to design engineered mutant insulins that have altered physiological properties for the treatment of special cases of diabetes.

Dorothy had the qualities of simplicity, directness, humility and a wisdom about human beings, their affairs and abilities. Above all she displayed a great joy for her work and in her life she was a constant source of inspiration and help to those around her. In particular, through her work at Somerville she has left a legacy of distinguished women scientists around the world, that includes Pauline Harrison, Jenny Glusker, Majorie Harding, Margaret Adams, Eleanor Dodson, Judith Howard and Carol Huber, among others. She married Thomas Hodgkin in 1937 and they had three children. Her children were still young when she was working on the structures of penicillin, vitamin B_{12} and other structures while at the same time carrying a substantial teaching load. Her tremendous intellectual powers coupled with a remarkable personality carried her through this busy time.

In Oxford she was never overtly political but operated through a quiet word in the right place. She was one of those responsible for attracting David Phillips to Oxford. In 1966 Sir Lawrence Bragg retired from his Directorship at the Royal Institution, London and a new home had to be found for his team who had just solved the first structure of an enzyme, lysozyme. Oxford created an *ad hominem* Professorship for David Phillips and Professor J.W. Pringle welcomed him to his Zoology Department. Thus the Laboratory of Molecular Biophysics in Oxford was established and the Hodgkin group became part of the Laboratory to the mutual benefit of both. I joined the Laboratory in 1967 and although I was never one of Dorothy's students, it was she who introduced me to Somerville and in an indirect way I may count myself as part of the succession.

She was a tireless fighter for peace, especially at a time when nuclear destruction during the Cold War appeared a real possibility. This work was pursued both through informal and formal organisations. The Pugwash movement was set up by Bertrand Russell and Albert Einstein in 1955 to promote East/West friendships and to seek co-operative solutions to disarmament and reduction of international tension. The movement was named after the small village in Nova Scotia where the first meetings took place. She became president of Pugwash in 1975 and her work was widely recognised. But she also worked through her personal contacts both for peace, for the Third World and for all those less fortunate.

She travelled widely and established many lasting friendships in the former Soviet Union, in Vietnam, in Africa, in Arab countries, in India and in China, as well as her contacts in Europe and the USA. Thomas was Director of the Institute of African Studies at the University of Ghana which meant that for several years in the 1960s she operated from both Ghana ("where there's rather more time to think") and Oxford. Indeed, she was in Ghana when the Nobel prize was announced.

J.D. Bernal, John Kendrew, Dorothy Hodgkin and David Phillips at the Royal Institution in 1965 just after the structure of lysozyme had been solved.

It was especially poignant but also a source of great joy that she was able, accompanied by her daughter Liz, to attend the International Union of Crystallography meeting in Beijing in August 1993. She first visited China in 1959 at a time when there were very few Western visitors. Her friendships established on this occasion were cemented later as Chinese scientists accomplished the synthesis of insulin and later their own crystal structure determination. The affection and respect shown on that final visit last year is echoed by all who knew her in the international community.

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1. Bernal, J.D. & Crowfoot, D. *Nature* **133**, 794–795 (1934).

I am grateful to M.J. Adams for information on the early days with insulin.

Dorothy Mary Crowfoot, chemist; born Cairo 12 May 1910; Fellow, Somerville College, Oxford 1936-1977; FRS 1947; Royal Society Wolfson Research Professor, Oxford University 1960-1977; Nobel Prize for Chemistry 1964; OM 1965; Chancellor, Bristol University 1970-1988; Fellow Wolfson College, Oxford 1977-1982; married 1937 Thomas Hodgkin (died 1982; two sons, one daughter); died 29 July 1994.