

# BIOGRAPHICAL MEMOIRS

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## **Dorothy Mary Crowfoot Hodgkin, O.M. 12 May 1910 – 29 July 1994**

Guy Dodson

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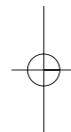
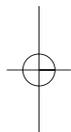
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12 May 1910 — 29 July 1994





*D.H. Hodgkin*

## DOROTHY MARY CROWFOOT HODGKIN, O.M.

12 May 1910 — 29 July 1994

Elected F.R.S. 1947

BY GUY DODSON, F.R.S.

*National Institute of Medical Research, The Ridgeway, Mill Hill,  
London NW7 1AA, UK*

### INTRODUCTION

Dorothy Hodgkin was an X-ray crystallographer whose scientific career began in the 1930s and finished in the 1990s; her research had a deep influence on modern crystallography, chemistry and biochemistry. She had a profound grasp of crystallography and a genius for applying its methods. Her research was driven by the conviction that the X-ray image was the best basis for understanding the chemistry and function of molecules.

There are accidents in all careers and in this Dorothy Hodgkin was no exception. The choice of her career was greatly influenced by her mother but her instincts for science, her intelligence and formidable tenacity made a career in science almost inevitable and, once a possibility, unstoppable. There are different ways of measuring scientists' gifts and the impact of their research. Dorothy Hodgkin began her research when X-ray crystallography was just beginning; there were therefore many opportunities. But her scientific accomplishments were exceptional by any standards. The crystal structures of cholesterol, penicillin, vitamin B<sub>12</sub> and insulin are enduring achievements and had an immediate impact on chemistry, biochemistry and medical science. Moreover, by demonstrating that complex chemical structures could be defined by X-ray analysis she changed the practice of analytical, degradative and synthetic chemistry. It was her use of computers that made this possible. Although Dorothy's laboratory was a centre for X-ray analysis and she was herself uncompromisingly dedicated to research, her warmth and kindness to the people in her laboratory made it an especially human place. Dorothy Hodgkin was unique in the combination of her authority in research, her humanity and her personal response to conflict and poverty. Finally, her students and young colleagues who came from overseas to study in her laboratory have created a worldwide legacy of research laboratories whose vigour and character are a testimony to her example and influence.

## EARLY LIFE

Dorothy was born on 12 May 1910 in Cairo, where her father, John Winter Crowfoot, was in the Egyptian Education Service. In 1916 he became Assistant Director of Education in the Sudan, a position that suited his general interests in ancient history, archaeology, the Middle East and education. In the Sudan Dorothy's mother Grace Mary (Molly), *née* Hood, found interests of her own. She helped to establish village schools and travelled with her husband on many trips and expeditions to encourage this. The flowers in the area were a particular delight and Dorothy's mother collected these on every opportunity; she made many botanical drawings which, with her collections, are now in Kew. Another of Molly Crowfoot's interests was weaving; this and her knowledge of fabrics led to her becoming an international expert in ancient textiles. These activities must have played their part in Dorothy's own appreciation of colours, fabrics and patterns, and set an example of serious study in the home.

Dorothy and her two younger sisters, Joan and Betty, were born in the Sudan, but during World War I they stayed with their grandparents near Worthing. Their parents remained until 1918 in the Sudan, where Diana, the fourth daughter, was born, and then they came back for a time. Unfortunately for family life, Dorothy's father returned to the Sudan but in 1922 Dorothy and her sister Joan, aged 12 and 11 respectively, were taken to visit their parents there. The visit to the Sudan made a tremendous impression, giving them their first direct experience of foreign people and cultures. It was here that Dorothy met Dr A.F. Joseph, a government chemist working in the Wellcome Laboratories in Khartoum, and a close friend of Dorothy's father. It was he who, on a subsequent visit in 1924, helped Dorothy to perform her first experiments in chemistry, trying to identify the minerals in the garden sand. She thought she had found manganese dioxide, but Dr Joseph, or Uncle Jo as the children called him, showed her that it was ilmenite, an ore not described in her books. (Many years later, Dorothy had great pleasure in learning that ilmenite was discovered on the moon.) On a later occasion Dr Joseph gave her a professional surveyor's kit for identifying minerals, which she used for 'many happy hours'. There is little doubt that this gift, and the visits he arranged to the Wellcome Laboratory in Khartoum, strengthened Dorothy's interest in chemistry and science. Other aspects of life in the Sudan were less happy: Dorothy was aware of the disease and poverty in the area, and her mother told her of the uprising in the local villages (sparked off by an increase in sugar prices) and its suppression by the British army.

## EARLY EDUCATION

Her early education was a little haphazard. For one year after the war, when the family was reunited, Dorothy's mother, wanting to get to know her children better, taught them (and two cousins) at home. It seems to have been a remarkably happy time with the children learning natural history, history, geography and poetry in very practical ways. They made their own books and illustrated them, they made solid three-dimensional maps (on a greenhouse floor) with rivers and lakes, collected flowers and plants, and observed butterflies and birds.

Dorothy's father believed that his daughters should attend local schools, like the Sudanese children for whose schooling he was responsible. With the family settled near Beccles, Dorothy—now aged 10—attended a local Parents National Educational Union class. Its book on chemistry began with experiments in crystal growing; these fascinated her. At 11 she was

enrolled at the nearby Sir John Leman School. Here there was no physics but the teaching in chemistry by Chris Deeley, a graduate from Manchester, Dorothy found inspiring. Both her parents recognized Dorothy's ability but her mother especially took a keen interest in her studies and her more scientific enthusiasms. She encouraged Dorothy's interest in chemistry, allowing her to purchase materials from the local chemist and to do analytical experiments at home. When Dorothy was 15, her mother gave her the books by Sir William Bragg, F.R.S., based on the Royal Institution Christmas lectures — 'Concerning the nature of things' and 'Old trades and new knowledge'. This was her introduction to X-ray diffraction and crystal structures. At the same time her interests in biochemistry were widened by Parsons's *Fundamentals of biochemistry* (Parsons 1924). Her father planned that she should go to Oxford, obviously to read science. Fortunately, Dorothy's family had the benefit of friendship with Margery Fry, then Principal of Somerville College. On hearing that Dorothy wished to study chemistry, Margery Fry's sister Isobel remarked, 'She wants to do science? Why, they'll practically pay her to come to Somerville.' More practical support was provided by her aunt, Dorothy Hood, who made Dorothy an allowance and helped with the fees. Although Dorothy flowered at the Sir John Leman School and came top in England in the School Certificate examinations, she still needed further qualifications to get to Oxford: Latin, a second science and more mathematics. She acquired these with help from her mother and various friends, took the College Entrance exam successfully and went to Somerville in 1928 to study chemistry.

#### AN UNDERGRADUATE AT OXFORD

It is characteristic of Dorothy's life that before she began her degree she accompanied her father on an archaeological expedition to Jerash in Trans-Jordan to excavate Byzantine churches. She enjoyed the whole experience and was delighted by the mosaic pavements, being especially struck by the symmetry constraints on the two-dimensional patterns. Dorothy made wonderfully detailed drawings of some of these, a commitment that took her a further two years to complete. One of these is shown in figure 1. However, her interest in archaeology did not distract her in the slightest from her plans to study chemistry.

Although Dorothy had a general interest in chemistry and biochemistry, she had decided to study X-ray crystallography. In her first year she attended a few lectures on crystallography given by Dr Barker, the elderly University Reader in Mineralogy. He feared that Dorothy was starting too soon and persuaded her to delay her studies for a year while she consolidated her chemistry. Unfortunately, Barker died soon afterwards, so her formal teaching in crystallography was delayed. However, she found the lectures by Robert (later Sir Robert) Robinson, F.R.S. (P.R.S. 1945–50), and C.N. (later Sir Cyril) Hinshelwood (F.R.S. 1929; P.R.S. 1955–60) very rewarding, Robinson's being particularly wonderful for their scope and the connections that they made in chemistry and biochemistry. Such giants as Sir Ernest (later Lord) Rutherford, F.R.S. (P.R.S. 1925–30), Niels Bohr, For.Mem.R.S., and Peter Debye (For.Mem.R.S. 1933) also occasionally lectured in Oxford, and made an immense impact on her, as did the lecture by J.D. Bernal (F.R.S. 1937) on the metallic state—the lecture was laced with X-ray crystallography.

There were also interesting contacts within the college and the university. Dorothy was quiet and apparently shy, but she made some long-lasting friendships, joined in with college life and dug with the archaeological society at Roman sites around Oxford. There were also



Figure 1. Mosaic in the Propylaea Church at Jerash. The figure was prepared for the report of the Joint Yale–British School Expeditions to Jerash, 1928–30, by J.W. Crowfoot and was drawn between 1918 and 1920 from sketches that Dorothy made on the expedition. It now resides in Yale University. (Reproduced from Crowfoot (1931).)

various ‘heroic’ figures, such as Dame Elizabeth Wordsworth, who were friends of her parents and who took an interest in her. Margery Fry’s ideas about society and the behaviour of nations coincided with those of Dorothy’s mother, and these Quaker values too had a long-lasting influence.

Dorothy completed her Part I with first-class honours. There were several options open to her for her Part II, a fourth-year research project, but she was anxious to return to crystallography. She was greatly encouraged in this by Dr Polly Porter, a Research Fellow at Somerville, who had worked for years measuring and cataloguing crystals. Though Dorothy was entranced by their beauty, she was itching to make the next step and, like W.L. (later Sir Lawrence) Bragg, F.R.S., to place the individual atoms. In 1929 she saw volume 25 of the *Transactions of the Faraday Society* with its papers by the Braggs, Goldschmidt, Lonsdale and Bernal; it opened her eyes to what was possible. Her tutor, Freddy Brewer, steered her to work with the newly appointed University Demonstrator in X-ray crystallography, H.M. (Tiny) Powell (F.R.S. 1953), who himself had only just set up a research laboratory. He had identified a very suitable project: the crystal structure of the dimethyl thallium halides. Dorothy had to synthesize and crystallize these compounds herself. She found that the best crystals were those containing bromide; they were tetragonal and big enough for X-ray diffraction data to be

measured reasonably easily. She deduced from the crystal symmetry and cell dimensions that the thallium and bromide ions had the same face-centred lattice as the sodium and chloride ions in common salt and that the two methyl groups were positioned on each side of the metal (3)\*. This was the first structural analysis of a metal–carbon bond; 27 years later she identified another example of much more surprising chemistry in the coenzyme B<sub>12</sub> (12). No calculations were done in these studies to verify the positions of the methyl groups by calculating the X-ray amplitudes and comparing these with the observed values. It is impossible to imagine Dorothy not doing such calculations later in her life.

After completing her degree, Dorothy was unclear what to do next. ‘Uncle’ Joseph knew of this and contacted a Cambridge friend, Professor T.M. Lowry, F.R.S., who had been involved in Bernal’s appointment and who had chaired the 1929 Faraday Discussion that had impressed Dorothy so much. Bernal was enthusiastic about having Dorothy in his laboratory, and Dorothy, after reading his recent studies on sterols, knew that this was exactly where she wanted to go.

#### RESEARCH AT CAMBRIDGE

Bernal’s omnivorous interests, powerful intelligence and original ideas about the determination of crystal structures made his laboratory a world centre for crystallography. X-ray diffraction was being used for the first time in conjunction with optical techniques to characterize all sorts of crystals, to deduce molecular masses and to analyse molecular dimensions. Dorothy herself has told how Bernal got her to organize his reprints, sort out the crystals in the laboratory and to tidy his desk. Typically she regarded these chores as useful, giving her an insight into what was going on and what needed to be done. The topic of her PhD thesis was a crystallographic investigation of steroid crystals, a continuation of Bernal’s research and attractive because of its chemical and medical importance. From the crystal studies, Bernal and Dorothy were able to deduce the sterol skeleton correctly but this led to conflicts with the chemists, her first experience in scientific disputes. The thesis did not prevent Dorothy from pursuing other interests: following Bernal’s own example of catholic interests, she studied minerals, metals, organic and inorganic molecules, proteins and viruses. All of this provided a first-class training (1, 4) at the perfect time and place.

One day in the early summer of 1934, Glen Millikan, an Oxford biochemist returning from Sweden, brought crystals of the enzyme pepsin grown by John Philpot in Svedberg’s laboratory in Stockholm, knowing that Bernal would love to look at them. Bernal examined them under the polarizing microscope and found that when removed from their mother liquor the crystals dried, whitened and lost birefringence. On exposure to X-rays these dried-out crystals gave no spots, only a vague blur. But he discovered that if the crystals were kept wet in a sealed capillary they remained clear and diffracted well, covering the film with a mass of reflections. On that particular day Dorothy was in London seeing a consultant about what proved to be rheumatic pains, the first diagnosis of the discomforts to come. When she saw Bernal’s photographs she realized their importance, and with Bernal leaving her to complete the experiments she worked intensively on characterizing the crystals and quite ignored medical instructions to rest. The diffraction pattern suggested that the pepsin molecule was ‘an

\* Numbers in this form refer to the bibliography at the end of the text.



Figure 2. Dorothy (left) at the 50th anniversary of the pepsin photograph, Cambridge, July 1984. Next to her are John Philpott, and Helen Megaw, whose glass capillaries were used in the pepsin experiment. (Photograph courtesy of Claudio Villa and Cyrus Chothia, F.R.S.)

oblate spheroid with diameters of *ca.* 35 and 25 Å arranged in hexagonal nets' and largely hydrated in the crystal. In spite of the molecule's size and complexity, the extent of the diffraction pattern showed that 'the arrangement of atoms inside the protein molecule is also of a perfectly definite kind' (2). This was the beginning of protein crystallography, and it was one of the most important scientific episodes in Dorothy's life. It was marked 50 years later by a gathering in Cambridge of many who were involved (see figure 2).

Dorothy has often been given the credit for this hugely important X-ray experiment but she always made it clear that it was Bernal who took the first photographs and had the critical insight to keep the crystal wet. Dorothy in her experiments with the crystals also observed that the X-ray reflections weakened with exposure to the radiation, a continuing problem with macromolecular crystals until the recent introduction of cryo-techniques. The question arose as to whether the radiation damage affected the enzyme's activity. Experiments showed that it remained active, proving that the loss of diffraction was due to damage to the crystal lattice, not to chemical and structural changes in the molecule.

Soon after Dorothy had arrived in Cambridge and started her PhD, Somerville College, Oxford, offered her a tutorial Fellowship, in some ways an attractive prospect and a welcome chance for secure employment. However, she was reluctant to accept it so soon after joining Bernal's laboratory, where she was experiencing the thrill of doing original research and being part of an exceptionally active group. Somerville was sympathetic, and shrewdly offered her two research years, one to be held in Cambridge and the second in Oxford. Sadly but realistically she accepted and returned to Oxford in 1934. Although she spent barely two years in Cambridge she had become a serious scientist utterly committed to doing research.

## FAMILY LIFE AT OXFORD

Oxford was to be her home for the rest of her working life. Early in 1937 Dorothy met Thomas Hodgkin while she was on a visit to the Royal Institution. They were both staying with Margery Fry, who was Thomas's cousin. It was a bad time for Thomas: he had been working in the civil service in Mandated Palestine but had fallen out with the administration over his support for Arab rights. He had resigned and been abruptly expelled. Now his future was uncertain and he was unsure about what he wanted to do. For Dorothy the situation was different: her position at Oxford was secure and she was establishing herself in the scientific community. Their friendship grew and for Dorothy there was the attraction of an intelligent, articulate and lively man whose social and political ideas were close to hers. He had a love and knowledge of literature and culture, a gift in conversation and approached life with a wonderful sense of fun. They were married in December 1937, by which time Thomas had been appointed very happily to the Workers' Education Association in Keele.

Dorothy continued to work in Oxford while Thomas built up a well-respected adult education programme in North Stafford. They began the habit of a lifetime—she and Thomas wrote to each other daily. Their first child, Luke, was born in 1938 but soon after this Dorothy developed a breast abscess and after a period of high fever developed acute rheumatoid arthritis. The pain and stiffness finally wore off but were to return later and become a chronic condition. A second child, Elizabeth, was born in 1941, and in 1946 Toby's arrival completed the family. During the war the family was relatively settled; they moved into the flat at 20c Bradmore Road in North Oxford, where Thomas's mother had lived and to which they would return many years later. A variety of family members, refugees and other friends provided the support that Dorothy needed as she got more active in research, inheriting Bernal's X-ray equipment and two of his students. Throughout this tense and worrying time Dorothy continued to work steadily, calculating Patterson functions with the insulin data, and writing. Later the penicillin programme, which was urgent and secret, brought considerable extra pressures.

In 1947 Dorothy was elected to the Fellowship of The Royal Society, the third woman to be so, a sign that she was now a recognized scientific figure. She had finally obtained a university post: a Demonstratorship that required her to do a little more teaching and provided a welcome extra £350 a year. In addition to these improved circumstances, Thomas moved to a post with the Oxford Delegacy for Extramural Studies. Dorothy's promotion to a Readership followed in 1955, and five years later she was awarded the Royal Society Wolfson Professorship. There were domestic upheavals precipitated by Thomas's decision in 1951 to resign his position to travel and study African history. These were largely solved in 1957 when Dorothy and Thomas moved to 94 Woodstock Road, a rambling Victorian house near the centre of Oxford. They were joined by Dorothy's sister, Joan Payne, who took charge of the housekeeping, and her five children. This made a household of three adults and eight children, who lived together in a happy and relaxed communal atmosphere. Both Dorothy and Thomas threw out generous invitations for lunch, dinner and parties and the house became a centre of the most varied and sometimes almost continuous hospitality. Everyone who came into Dorothy and Thomas's orbit would mingle at these functions: crystallographers, poets, historians, writers and the teenagers and their friends. They were expected to get on, and they mostly did. This was partly due to Thomas's expansive and cheerful personality and his obvious interest in people, but Dorothy's presence was always important and her tact was sometimes needed. For the crystallographers these occasions certainly helped to bring a family feeling to the atmosphere of the laboratory.

In 1970 Thomas 'retired' to Crab Mill, his parents' house in the village of Ilmington, while Dorothy continued working in Oxford living at Woodstock Road until 1977, when she herself retired. This brought changes: a return to Bradmore Road and, with Thomas becoming increasingly unwell, more time at Ilmington. Thomas's illness, however, did not take away his intellectual vigour, his ability to entertain or his companionship. When he died in 1982 Dorothy was deeply affected. She lost weight and her arthritis became worse, but even though exercise and travel were more difficult she continued to do research, mostly giving thought to the insulin refinement calculations but also carrying out the occasional analysis (for example, *cis* Piloty compounds). She was still passionately interested in science and was in great demand as a speaker, and as the President of the Pugwash Movement she still had considerable commitments. In spite of her frailty she attended the International Union of Crystallography (IUCr) Congresses in Bordeaux in 1990 and in Beijing in 1993. Particularly in China this was seen as a demonstration of the importance that she attached to international meetings and to developing countries. The Congress at Beijing was an emotional occasion; many realized that this would probably be the last major crystallographic function she would attend and the last time that she would visit China. After returning from China, Dorothy spent her time at Crab Mill, living quietly, often with her daughter Liz. After a fall, she died at home with her family on 29 July 1994.

#### RESEARCH AT OXFORD: LABORATORY LIFE

After returning to Oxford from Cambridge, Dorothy soon organized her own laboratory and took on undergraduate teaching and supervision. In the college she was anxious to recruit science students, and worked hard to achieve this. She was a demanding teacher and in tutorials could be distant, but she was a wonderful chemist and could bring an unusually broad perspective to her students.

Because the Somerville fellowship was not a university post there was no support for research; consequently, Dorothy needed help to set up a laboratory. Professor H.L. Bowman in the Department of Chemistry offered her space in the Crystallography Laboratory, and the organic chemist Professor (later Sir) Robert Robinson, who had recognized the importance of crystallography for chemistry (at least as Bernal did it), helped her to write her first research application, to ICI for £500 for the purchase of X-ray equipment. By the time that Dorothy arrived in Oxford the laboratory was ready, shared with Tiny Powell, her former supervisor, in the Old University Museum. This is a cavernous, Gothic building and a somewhat gloomy and odd environment for a crystallography laboratory.

From its beginning, the laboratory was run most informally, lifelong friendships were established and the occasional marriage took place. The use of first names was encouraged; Dorothy greeted me with the remark that she preferred to follow the American custom and use first names—I suspect that this tradition went back to her time at Cambridge in Bernal's laboratory. Many have noted the casual atmosphere and interpreted this as disorder. However, Dorothy's own beliefs required a rigorous approach to crystallography and structure determination. The atmosphere reflected her passionate belief that molecular structure and chemistry were important and that the crystallographic studies really mattered. In the 1940s and 1950s Dorothy did a good deal of experimental work. She loved using a mineralogical microscope for examining a crystal and, as long as her arthritic hands let her, she would mount crystals,

take and develop X-ray photographs and then from the diffraction pattern make deductions to great effect about the space group and molecular packing.

World War II brought great changes to her research. Bernal and others were diverted into war-related research, and Oxford was left as one of the few functioning crystallographic laboratories in the UK. Several people moved to Oxford from Bernal's group and in addition his X-ray equipment, bought by the Rockefeller Foundation, was at his request sent on from Birkbeck to Dorothy's laboratory. The Rockefeller Foundation provided her with funding throughout the war, allowing her to continue her research into insulin and, later on, to investigate the penicillin crystals. These were extremely difficult times and the Foundation acted generously and most sympathetically to her requests that were really fairly modest. On one occasion she was written to immediately after her request for funds had been approved in order 'to ease her mind' because a formal announcement would take some time. In the middle of the war this was kindness indeed. It is hard to see how Dorothy could have done very much in these extremely difficult conditions without Rockefeller funds. In fact the Rockefeller Foundation's support for Oxford, Lawrence Bragg's group in Cambridge and other groups in the UK ensured that an active research community doing structural research in biology was maintained. Although small, this community was the basis for the phenomenal research that followed in the 1950s and 1960s.

The reports on the visits made by Gerard Pomerat, a Rockefeller officer during and after the war, describe a happy, well-managed and effective research group—'under good strong scientific discipline by their gentle lady boss' and 'a lovely small show'. This is a description that in many ways still applied in later years when her laboratory expanded. As she got older she was less adept physically, but she remained closely involved in the work, moving about the laboratory from desk to desk discussing progress and problems. Whenever new crystals appeared or there were new Patterson or electron-density maps, Dorothy was in her element, analysing and indicating significant features and what might be done next. If interpretations were elusive, Dorothy would often retreat into an absorbed state, humming hymns and working with utter concentration until interrupted, or she became simply too tired.

In 1960 Tiny Powell, who was in charge of Chemical Crystallography, and Dorothy moved to the newly built Chemical Crystallography laboratories in the Inorganic Chemistry building. Six years later, David (later Lord) Phillips (F.R.S. 1967) came to Oxford and established the Laboratory of Molecular Biophysics in the Zoology Department. Dorothy's insulin group straight away became closely associated with Molecular Biophysics, first in Old Physiology as a temporary measure and then in the early 1970s when her whole group moved to a set of rooms in the Department of Experimental Psychology in the new Zoology building. Although this manoeuvre had the two groups on opposite sides of the building, they developed the very close research and social contacts that Dorothy had always hoped for. After her retirement she returned to Chemical Crystallography, now in the old Agricultural Sciences building, to join Keith Prout. All these movements did not seem to distract her: wherever her laboratory was located she concentrated on the task at hand and as far as I am aware never complained about the sometimes quite real inconvenience of her research arrangements. And she was always very much part of the Oxford scene, lunching at Halifax House, attending seminars in many of the departments and turning up at university functions.

As the two leading Oxford crystallographers, and colleagues for over 40 years, Dorothy and Tiny Powell's relations were of some importance. Although both had similar social and political views and were sympathetic people, they had rather different approaches to life and research and



Figure 3. Chemical Crystallography *ca.* 1951. Dorothy is sitting on the middle row, second from left; on her right is Frank Welch, the laboratory technician who spent his whole working life in this laboratory. David Sayre is standing on the far right and James Raynor is two places to his right. In the front row (from left to right) are Derek Holmes, Geoffrey Pitt, John Anthony (Tony) Jarvis and Pauline Harrison (*née* Cowan).

they frequently failed to communicate. Certainly, Dorothy could have a rather casual approach to administration (see McLauchlan (2000), pp. 437–438) that sometimes made difficulties for Tiny, who was the senior in university terms and was formally responsible for Chemical Crystallography. One episode that illustrates this tension between these two very likeable people relates to the weighty Victorian key to the Museum, where Chemical Crystallography was housed before being in Inorganic Chemistry. On moving, Tiny was responsible for collecting and returning all keys, but Dorothy had lost hers, causing him some bother. Years later I was with Dorothy in her room when the key showed up, and she giggled rather guiltily and undertook to return it at last to Tiny. She must have forgotten because some weeks later when we needed to go to Physics, Dorothy, who found walking difficult, remembered the key to the Museum and decided to use it to make a nice short cut. Unfortunately, Tiny saw Dorothy unlocking the Museum door—‘God’, she said, ‘I’d told him I’d lost this key and now look at what he’s seen. He’ll never believe I’d really lost it.’ In spite of these occasional frictions there was nevertheless real mutual respect: for example, Dorothy’s Nobel Prize gave Tiny great delight. Figure 3 shows a photograph of Chemical Crystallography taken outside the University Museum.

Dorothy’s research papers and the accounts of her experiments are surprisingly easy to read in spite of their crystallographic content and the complexity of the molecules studied. The vita-

min  $B_{12}$  papers in particular are outstanding and are a delight to read. All the calculations that a crystallographer needs are described and the thinking and decisions made in the course of the analysis come through in an illuminating way. The figures are often beautifully prepared and illustrate wonderfully the connections between the Patterson and electron-density maps and the atomic positions deduced from them. Some of the papers include electron-density maps drawn on translucent paper; these sit over the drawings of the atomic positions, revealing graphically the nature of the structure and the evidence that it was based on (see figure 4; (11)).

These papers made a great impression on me, so much so that David Hall, my supervisor in Auckland, perhaps tired of my admiration, remarked, 'If you think so much of the bloody woman why don't you write to her and ask her for a job?'. Which I did.

There were many visitors to the laboratory. From the beginning these included all the major crystallographers: the Braggs, J.D. (Sage) Bernal, K.Y. (later Dame Kathleen) Lonsdale, F.R.S., Max Perutz, F.R.S., and later of course her own former students and colleagues, often themselves distinguished. On these occasions Dorothy would spread the news around the laboratory so that all were ready for a seminar and the discussions that might begin in the laboratory but often drifted to pubs and her home. Such visits were frequent enough perhaps to explain Dorothy's not organizing any formal seminar programme, although of course some of her colleagues did. Another factor was Dorothy's own enthusiasm for going to seminars in other departments of the university, and she rather expected people to follow her example and attend these.

With the award of the Nobel Prize in 1964 Dorothy was much more in the scientific and public eye. This, and her absences to Ghana with Thomas, who was then Director of the Institute for African Studies in Accra, brought new demands on her time and put extra responsibilities on the more experienced members of the laboratory. This was less of a problem than it might have been, because Dorothy frequently wrote long and marvellously clear letters with advice, ideas and questions. Moreover, she seemed to be able to organize experienced visitors, such as Sivaraj Ramaseshan from India and Boris Kamemar from Yugoslavia, who could help with any supervision. Consequently, in her absence the laboratory generally continued to work effectively. Dorothy usually enjoyed travel and the experience of visiting other laboratories. Many friends were made on these trips and many quote her undemanding and friendly presence and the penetrating crystallographic comments she would make, always delivered it seems with a characteristic hesitancy. She would often come back with ideas. One critical piece of news for the insulin research came from Uppsala, where Björn Tillander and Bror Strandberg had found they could extract zinc from carbonic anhydrase crystals and replace it with other metal ions. Dorothy realized that this was an experiment that might work on insulin (it did), and told us immediately she got back.

From the various accounts of people who have worked with her and from my own experience, Dorothy was generally very easy to work with, unhesitatingly generous and open to discussion, usually able to come up with acute technical advice and with an extraordinarily shrewd eye for mistakes in the crystallography. Successful work was greeted with delight, while failures or mistakes she tried to treat constructively, often making generous allowances, sometimes perhaps too generous. This seemed to pay off but when Dorothy detected too much lack of interest or laziness she could be quietly severe and reduce some of the idle to pale wrecks. However, she did not like to be authoritarian and would typically begin her usually excellent advice with such gentle devices as 'It might be an idea to try...'. But it was understood that the soft nature of her remarks should not be misinterpreted—this was advice to be followed!

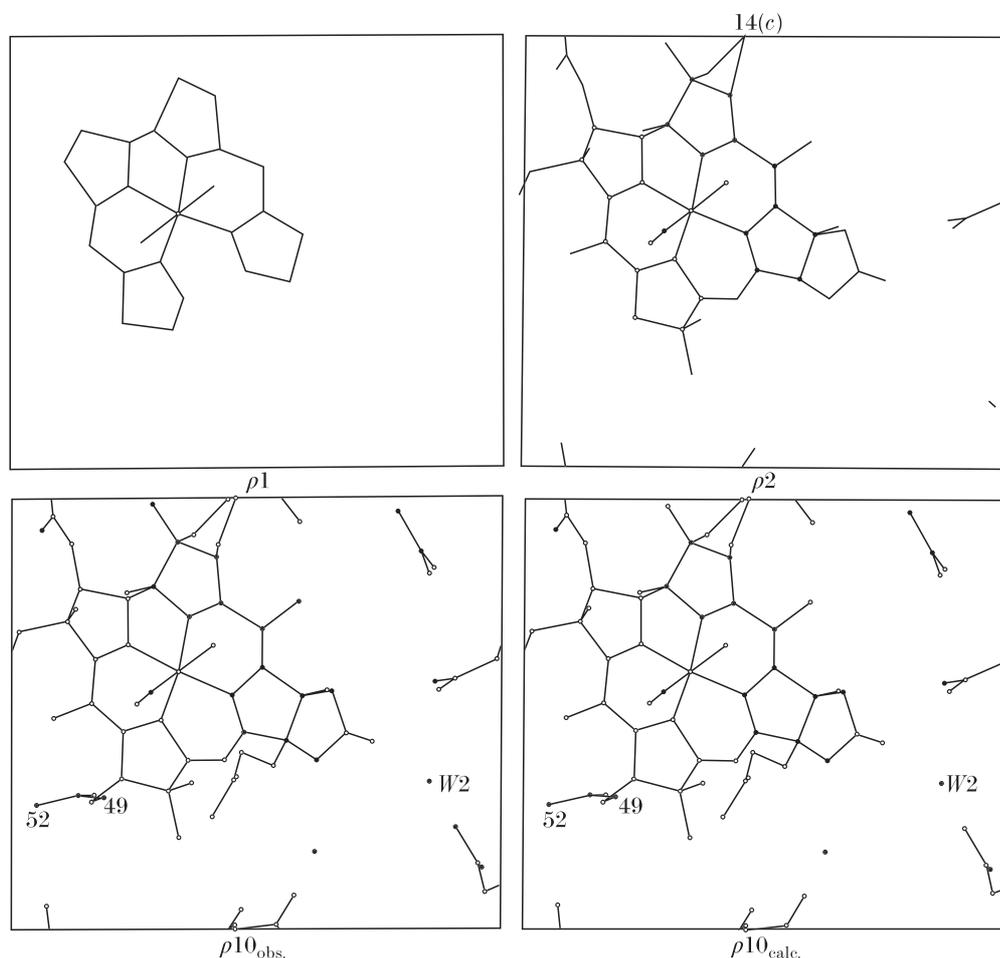


Figure 4. The electron density at the corrin ring in the first two calculations ( $\rho_1$  and  $\rho_2$ ) and the calculations at cycle 10 ( $\rho_{10_{\text{obs}}}$  and  $\rho_{10_{\text{calc}}}$ ). The density shown is for sections  $x = 6/60$  and  $x = 7/60$  on transparent material, which can be placed over the corrin moiety and nearby structure, as recognized at the different stages. The figures illustrate the improvement in the definition of the atoms on the corrin and those nearby, including some solvent molecules (W2), as the analysis progressed. The comparison of the  $\rho_{10_{\text{obs}}}$  (using observed structure amplitudes) and  $\rho_{10_{\text{calc}}}$  (using structure amplitudes calculated from the atomic parameters) shows that weak features such as H atoms could be detected, for example at W2, C49. (This image is taken from Hodgkin *et al.* (1959).)

Many young crystallographers and chemists came to Dorothy's laboratory and a good many of them have had very successful research careers. She gave excellent advice on their futures and was often able to steer her young crystallographers to first-class laboratories in the UK, USA and Europe. Dorothy had many crystallographers from abroad in her group; often there were more of these than from the UK. On the whole, she preferred people to return to their homes and start their own research; many did, persuaded by her confidence in them. Thus, one of her legacies is the protein crystallographic research established largely by her former students and colleagues in India, China, Canada and New Zealand.

Her tenacity was one of her most obvious qualities. It was a feature of the insulin research but it applied to all her major projects. It came from believing that the problem could be done

and that it mattered; in addition, she was naturally optimistic and had exceptional judgement on crystallographic methods and their applicability. Nevertheless she was quite conscious of the failures, remarking on a number of occasions that she might have had successes but she spent most of her time failing. These successes were no doubt another important factor in her morale. However, interesting in this connection is an episode, described in a letter to Max Perutz from David Sayre. It occurred while David was driving with Dorothy back from Cambridge in 1950 after seeing Max. David recalls that he remarked to Dorothy that by tackling soluble problems such as cholesterol and penicillin she had been able to achieve success, unlike Max and J.C. (later Sir John) Kendrew (F.R.S. 1960), who were still struggling and apparently getting nowhere with haemoglobin and myoglobin. Dorothy burst out with frustration over the slowness of the insulin research and her not getting on with it fast enough—while Max and John were working away on their proteins, she was not. It was as though she was regretting being distracted from insulin. Not everyone realized that Dorothy had this fierce commitment to insulin. This moment of rare frustration, witnessed by David Sayre, was a reflection of that commitment, but this reaction was never sensed by me, nor as far as I am aware by any others working in the laboratory.

Dorothy was always a person whom one could turn to with problems. As just one example she gave real support to Max Perutz in the years when there were simply no encouraging results from his haemoglobin research, or for that matter from her own insulin research. Although there were long periods when the research was just a slog, as far as one can tell she was always confident about the final outcome of the insulin research and protein research generally and this confidence she would pass on. Max Perutz has described the enthusiasm that Dorothy brought to his research and remembered the advice she gave him when he had solved the projection of the haemoglobin structure with one derivative: get a second, use the Bijvoet effect and calculate the structure in three dimensions. There is no better description of Dorothy as a person and a scientist than that in Max Perutz's address at her memorial service in Oxford in 1995.

Dorothy was more Christian in word and deed than many believers I have known. She radiated love: for chemistry, her family, her friends, her students, her crystals and her college to which she generously gave part of her Nobel Prize for the support of students and for the college staff. Her love was combined with a brilliant mind and an iron will to succeed, regardless of her frail and later severely crippled body. There was magic about her person. She had no enemies, not even amongst those whose scientific theories she demolished or whose political views she opposed. She was very forgiving. Just as her X-ray cameras bared the intrinsic beauty beneath the rough surface of things, so the warmth and gentleness of her approach to people uncovered in everyone, even the most hardened scientific crook, some hidden kernel of goodness. It was marvellous to have her drop in on you in your lab, like the Spring. She brought interest and enthusiasm for your work making you feel it was really important, and more often than not she would point out something relevant that you had overlooked, because she knew more about your problem and the ways of solving it than you did yourself. At scientific meetings she would seem lost in a dream, until she suddenly came out with a penetrating remark, usually made in diffident tone of voice, and followed by a little laugh, as if wanting to excuse herself for having put everyone else to shame.

## RESEARCH

### *Crystallographic methods*

Dorothy was an excellent experimentalist and from the very beginning of her research she was interested in the practicalities of crystallography. She realized that X-ray diffraction could

locate atomic positions but to get this information the reflections had to be indexed and their intensities measured. This required the reconstruction of the diffraction geometry, a complicated calculation that led to her developing a convenient method for indexing Weissenberg camera photographs. The method was published in 1935; it was the first paper she wrote on her own (4).

In the 1940 and 1950s the determination of small-molecule crystal structures depended on heavy-atom methods or a trial-and-error approach. However, the development of direct methods in the 1950s and 1960s has made the structure determination of small molecules routine. David Sayre, while a student in Dorothy's laboratory in 1949, derived the convolution and triplet relationships that lie at the heart of these methods. He then used the equations to solve the structure of the amino acid hydroxyproline (Sayre 1952). It is a little odd that in Dorothy's writings there is little reference to this fundamental discovery. However, it was clear from her conversations and reports that she realized its importance and was very proud that the Sayre equation was discovered and first applied in her laboratory. Dorothy's nervousness about her mathematics might explain in part her reticence about the discovery, but Lawrence Bragg, who had a deep mathematical grasp, had a similar attitude. It is perhaps more likely that this theoretical method appealed less because it had no structural character, unlike the Patterson and heavy-atom-phasing approach that in her hands was so very successful. Many years later, David Sayre returned to Oxford to apply direct methods to the 2Zn insulin data. This exercise was enthusiastically supported by Dorothy, who again found herself involved with calculations that pushed the available computing (at the Atlas Laboratory) to its limits.

It was widely believed before 1951 that it was not possible to distinguish between optical isomers by X-ray analysis. However, Bijvoet showed that the Friedel equivalence of the Miller indices  $h,k,l$  and  $-h,-k,-l$  normally seen in diffraction patterns can be broken if the crystal contains atoms that have an absorption edge near the wavelength used. His study on D-tartrate salt (the same salt investigated by Pasteur in his experiments on optical activity) defined the chiral stereochemistry, incidentally showing that the chemist's arbitrary definition was by chance correct. This physics was fundamental to chemistry and biochemistry and it greatly impressed Dorothy (Bijvoet *et al.* 1951). She also realized that anomalous scattering effects can provide information about phases and hence could help solve crystal structures.

Intensity differences in Friedel pairs had been noted in some of the early vitamin B<sub>12</sub> X-ray photographs and had caused some puzzlement. Dorothy once told me that her failure to explain these was still an embarrassment; she had just been too casual. Once understood, thanks to Bijvoet, the effects were exploited, with notable success by Venketasan and David Dale in their analysis of the aquo-cyanide of the vitamin B<sub>12</sub> nucleus. It was quickly realized that, for a small protein such as insulin, anomalous scattering effects were an excellent indication that a heavy atom was present in the crystal and could be used in screening the crystals for useful substitution. Even more important, these anomalous effects proved crucial in the solution of the insulin structure because they provided the data for phasing the reflections from the rhombohedral 2Zn insulin crystal. The anomalous scattering effects from the lead- and uranium-containing rhombohedral insulin crystals were measured. When combined with the isomorphous differences they gave an estimate of the heavy atom contribution  $F_h$ . Dorothy's son Luke and Eleanor Collier (later Dodson) helped Marjorie Harding in the original development of this idea. Even though approximate, the  $F_h$  term was essential for refining heavy-atom parameters accurately and it became widely used in three-dimensional calculations (Dodson & Vijayan 1971). Dorothy was not an author on this paper, as she was not on most technical

papers. However, it should be understood that she played a catalytic role in initiating the research and provided valuable advice all the way through this study, just as she did on many of the other more technical papers. Essentially the same equations combining the isomorphous and anomalous differences were developed independently and at the same time by Brian Matthews and Gopal Kartha, illustrating the need to estimate  $F_h$  in other laboratories (Matthews 1966). Synchrotron radiation, which is tunable, is an ideal source for producing anomalous scattering. It is pleasing to see that the exploitation of Friedel differences obtained from this radiation has now become a most important method for phase determination in protein crystallography.

When insulin's structure was solved in 1969 the atomic parameters of small-molecule crystal structures were routinely refined by using least-squares minimization to obtain the best fit between observed and calculated amplitudes. To refine atomic parameters for protein molecules was very difficult; the resolution of the crystallographic data was usually limited, with a much lower ratio of observations to parameters, and the problem was further compounded by large statistical and systematic errors in the measured structure amplitudes. Nevertheless, Dorothy always felt it essential to attempt such a refinement, following as far as possible the conventions of small-molecule crystallography, to identify errors and to get reasonably accurate coordinates as a basis for interpreting the molecule's interactions and chemistry. John Rollett, Neil Isaacs and Eleanor Dodson were somewhat sceptically drawn into this important issue. However, they found that the least-squares minimization approach became tractable when stereochemical restraints were added as extra 'observations' and that this led to well-behaved refinement. This made it possible to refine insulin and proteins in a physically sensible way and has become another standard method in macromolecular crystallography (Dodson *et al.* 1976).

#### Computing

At the heart of X-ray crystallography is the electron-density map generated by the Fourier summation of phased structure amplitudes with the individual atoms positioned at its peaks. Dorothy had long used electron-density maps to locate atoms, but for all but very small molecules the calculations of the phases by Fourier summations were painfully slow procedures even when limited to projections. The Beevers–Lipson strips that Dorothy bought in 1935 provided a very convenient method for the summations, but these still required summing by hand and were too limited for three-dimensional calculations on medium-sized molecules. For the penicillin analysis Dorothy took advantage of the Scientific Computing Service, a small computational organization set up for various government purposes by L.J. Comrie (F.R.S. 1950). He was a pioneer in the application of commercial calculators for scientific research and had met Dorothy in an X-ray Analysis Group Meeting during the war. The calculations were funded by the MRC and performed by Dr G. Hey on a punched card system used by the government for convoy planning. Conveniently it could be easily adapted to Fourier summations by following the strategy exploited in the Beever–Lipson strips. Even though there were frustrating waits for time to become free, the computations enormously speeded up the later phases of the research. This was particularly important when penicillin's chemical structure became a matter of contention and three-dimensional calculations were needed.

From this time on, Dorothy realized that computing was absolutely essential if crystallography were to realize its potential in chemical and protein studies, and she was on the alert for alternative computing arrangements. Insulin and vitamin B<sub>12</sub> Patterson functions were calculated on the Hollerith device again with Dr Comrie, whereas the National Physical Laboratory

also took on the later vitamin B<sub>12</sub> calculations. The University of Oxford recognized that computers were going to prove essential for many research projects. Dorothy, as the biggest user whose demands for very large calculations were continuously increasing, was asked to chair a committee to investigate the university's requirements for scientific computing. They recommended that a properly staffed computing laboratory should be established.

Dorothy knew from the beginning of her studies on vitamin B<sub>12</sub> that computing was critical. Initially the B<sub>12</sub> maps were computed on hand calculators and the Hollerith punched-card machine, as for the penicillin studies. However, the B<sub>12</sub> calculations were orders of magnitude greater and would have taken years to complete. This potential bottleneck was solved by Ken Trueblood, a crystallographer from the University of California, Los Angeles (UCLA), who was developing software for SWAC, one of the most advanced computers of the time, which had been established by the Bureau of Standards at UCLA. Ken Trueblood and his colleagues Mayer, Sparks, Prosen and Kruse had written programs for three-dimensional Fourier summations and wanted to test them on unknown structures. He met Dorothy while visiting Jack Dunitz (F.R.S. 1974) at Oxford and offered his computational resources to help with the B<sub>12</sub> calculations, truly a 'marvellous' development. After a trial calculation on calciferol, Dorothy was convinced. This collaboration meant that the analysis was completed in the relatively short time of about two years, making it a landmark in crystallography for this reason as well. Ken Trueblood has given a blow-by-blow account of these calculations through the letters and cables that passed between Oxford and UCLA (Trueblood 1981).

## X-RAY ANALYSIS OF CRYSTAL STRUCTURES

### *Cholesterol and steroid structure*

The sterols first caught Dorothy's interest when, as an undergraduate, she heard a lecture by I.M. Heilbron (F.R.S. 1931) on their chemical structure. Bernal's optical and crystallographic investigations on sterols had led him to propose a long thin molecule, very different from the model proposed by A. Windaus and H.O. Wieland (F.R.S. 1931) and the chemists. This was precisely the sort of application of X-ray analysis that Dorothy wanted to perform, with the added interest that it was medically important. For her thesis she investigated sterols using crystallographic methods. With Bernal she examined a series of related sterol compounds, determining their space groups, cell dimensions and molecular masses. The list is impressive: cholesterol, ergosterol, pyrocalciferol, oesterone, testosterone, androsterone, progesterone, and many modifications and derivatives. From the crystal data, and from the inspection of the low-angle X-ray intensities, it seemed that all these molecules had an extended skeleton. The chemists finally accepted the Bernal model, persuaded by the strengthening crystallographic arguments (which were, of course, quite new to them) and by their own chemical thinking. Dorothy records in her memoirs of Bernal how Professor Elizabeth Dane, working with Wieland, one night decided that the elongated ring sterol structure was correct but that when she went in in the morning to present her arguments, she found him with a letter from Bernal describing essentially that same formula.

However, it was clear that to resolve these structural questions with certainty and to establish chiral detail it was essential to determine the atomic positions, something that Dorothy had been wanting to do since a student in Oxford. The methods for this were understood. William Bragg had described in his 1915 Bakerian Lecture that the X-ray amplitudes were coefficients

of a Fourier series whose summation generated the atoms in the crystal cell; in the late 1920s his son, Lawrence Bragg, applied the Fourier principle successfully to diopside, using all the reflections from the principal zones; Kathleen Lonsdale's experiments had shown that it was possible to locate and refine atomic positions in small aromatic molecules. The intensities of the X-ray reflections used in these calculations were measured with reasonable accuracy; the difficulty was that the phase associated with each amplitude in the Fourier summation was lost in diffraction. There were, in principle, experimental solutions to this barrier, the so-called phase problem. One was isomorphous replacement, the second the introduction of a heavy atom whose scattering would dominate the total scattering from the crystal and simplify the phasing calculations. Solving the phase by such methods was the only hope but in those days was only achievable in very simple systems and usually by trial-and-error methods.

It was Dorothy's intention to continue her research into sterol structure at Oxford by completing the analysis on cholesterol iodide that had been part of her PhD thesis. There were available some rather nice crystals of cholesterol iodide that Dorothy had grown from material provided by Heilbron's laboratory. One of the happier consequences of the war was that Bernal's new X-ray equipment had come to her laboratory, together with some students and associates. One of these students was Harry Carlisle, who had been investigating sterol structures in Birkbeck. With him Dorothy had the assistance she needed to take on the analysis of the crystals. In her 1945 paper describing the structure Dorothy stated, 'The present analysis of cholesterol iodide is an attempt to determine the detailed structure of the sterol skeleton using as little chemical information as possible'. The solution started from the iodine atom, much the heaviest atom in the molecule. There were two closely related crystal forms, both of which were analysed. The iodine positions were located by Patterson methods and an electron-density map of the projected molecule was calculated by using the iodine phases, another enormous job. The two-dimensional maps revealed almost all the atoms in the molecule but of course the stereochemistry was lost. The calculation of the complete three-dimensional Fourier map was impossibly onerous. Instead, Dorothy and Harry Carlisle calculated the electron density only along lines normal to the projection through each of the projected atoms. The use of line syntheses was a clever approach, still a major exercise but possible. The calculations located the carbon atoms with reasonable accuracy. Their positions confirmed the molecule's chemical structure and gave accurate dimensions and stereochemical configurations. There was an interesting distortion produced by the double bond at C5–C6 only detectable by X-ray diffraction. However, they were not able to determine the molecule's absolute hand and in fact guessed it wrongly.

This study made a great impact, despite the war, and was the first of Dorothy's crystallographic triumphs. It was the first three-dimensional study of a complex organic molecule and it demonstrated crystallography's potential for resolving chemical and chiral features. Over the following 30 years Dorothy continued to investigate steroids in a consistent but occasional way, tidying up questions of conformation and chirality and investigating structural relationships between the different molecules. There were studies on calciferol, lumisterol, bromomirestrol and suprasterol II. Calciferol was a special problem. Dorothy was very anxious to solve its structure because she believed, with others such as Jack Dunitz, that Bernal's general formulation for sterols did not apply. Its unusual extended ring structure was determined in a projection in 1948; the three-dimensional structure of a derivative was solved in 1957 (9); the structure of the original crystals themselves was solved only in 1994 with the use of synchrotron radiation (Leban *et al.* 1994).

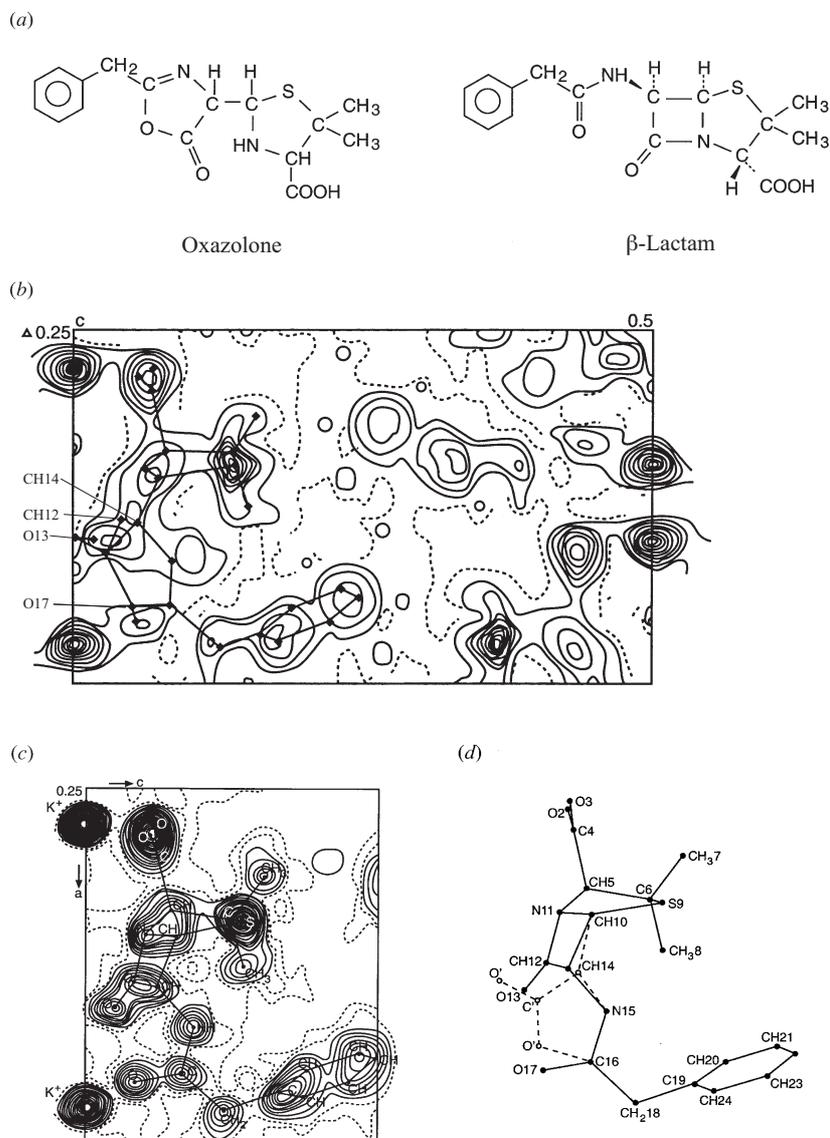


Figure 5. Stages in the determination of the crystal structure of penicillin. (a) The oxazolone and  $\beta$ -lactam structures. There are significant differences in their chemical properties. The atomic positions of the amide moiety of the  $\beta$ -lactam are not so dissimilar; the main difference is the C–N amide bond in the  $\beta$ -lactam and the ether linkage O–C in the oxazolone. (b) The electron density of rubidium benzylpenicillin in the *hol* projection, calculated with 114 terms. At this stage the evidence for the nature of the penicillin moiety is inconclusive. The density, however, does suggest moves in the atomic positions away from the oxazolone model used in the phasing (note O13 and O17—figure modified) towards the  $\beta$ -lactam arrangement. (c) The final electron-density map in the *hol* projection of potassium phenyl penicillin. This is isomorphous to the crystal of the rubidium salt. The evidence for the  $\beta$ -lactam ring is conclusive. (d) Diagram to illustrate the movement of atomic positions necessary to change a  $\beta$ -lactam to an oxazolone structure. Filled circles are atoms belonging to the  $\beta$ -lactam structure; open circles are atoms belonging to the oxazolone structure formed by moving atoms CH12, CH14, O13 and O17. (Parts (b)–(d) of this figure are taken from *The Chemistry of penicillin* (8).)

*Penicillin and antibiotics*

The story of penicillin again illustrates the capacity of X-ray analysis to answer chemical questions. Dorothy knew about penicillin from E.B. (later Sir Ernst) Chain, F.R.S., H.W. (later Lord) Florey (F.R.S. 1941; P.R.S. 1960–65), E.P. (later Sir Edward) Abraham (F.R.S. 1958), and the others working on the project, and Chain had remarked once: ‘Some day we will have crystals for you’. But crystals did not grow from the barium salt that was available. Several degradation products were crystallized and examined, leading to the realization that there must be sulphur present—another demonstration of the useful information that could come from X-ray investigation. The combination of these and the chemical studies produced two possible candidate structures for the molecule: a  $\beta$ -lactam or an oxazolone; their structures are illustrated in figure 5. After advice that crystals of the sodium benzyl penicillin salt had been obtained at Squibb by Dr Wintersteiner, crystals were grown of the sodium salt of the Oxford preparation, which had an aliphatic 2-pentenyl side chain. Because the benzyl penicillin crystals were simpler, it was decided to pursue those and accordingly a sample, with instructions for crystallization, was sent to Oxford through the good offices of Sir Henry Dale, F.R.S. (P.R.S. 1940–45), and Kathleen Lonsdale.

The analysis started immediately and, anticipating the need for phases, Dorothy arranged to get crystals with the other alkali metal salts. Unfortunately, only the potassium and rubidium series were isomorphous; the sodium, although related, was different. The structural programme became complex: there were three sets of data and more than one way of proceeding. The urgency of the research made a division of labour desirable and it was agreed that Dorothy should continue with Barbara Low to study the isomorphous potassium and rubidium series. In parallel, Charles Bunn (F.R.S. 1967) at ICI started experiments on the crystallographically simpler sodium salt with Bragg’s old X-ray microscope using the ‘fly’s eye’ technique. Dorothy, with her sterol experience, soon came to the conclusion that penicillin was compact and folded up. The models were given to Bunn and his assistant Anne Turner-Jones to try while Dorothy and Barbara Low struggled to interpret the electron-density map projections that were greatly distorted by the special locations of the metal ions. Although the initial experiments in both laboratories looked disappointing, when their maps were compared Dorothy recognized common features, especially the benzene ring, and saw that her assumptions were wrong about the sodium and rubidium being in similar positions.

The comparisons of the maps led to a new model in which both the sulphur and benzene ring were located with the molecule still folded in an oxazolone arrangement. Although the atomic positions in the oxazolone and  $\beta$ -lactam rings are not very different (see figure 5*a*), the calculations forced both laboratories to the conclusion that the oxazolone structure was not possible and that a  $\beta$ -lactam ring was much more likely. Further calculations with the essentially correct structure confirmed this, but because they were done only in projection and because of the ‘intense local opposition’, Dorothy was cautious about it when she presented her results in London at a penicillin meeting held in February 1945. By May, however, the three-dimensional map had been calculated and it was obvious that penicillin had the  $\beta$ -lactam structure.

According to E.P. Abraham, the Merck group in October 1943 had considered the  $\beta$ -lactam structure to be possible but did not favour it. R.B. Woodward (For.Mem.R.S. 1956) in Harvard had decided from thermochemical evidence in September 1944 that penicillin had a  $\beta$ -lactam structure. Exactly who got there first is not clear; Dorothy got her results by analysis of the electron density independently of the chemists and because it took some years to synthesize

penicillin she had the satisfaction of being the first to demonstrate directly and unequivocally the presence of a  $\beta$ -lactam ring. Quoting E.P. Abrahams again, she 'silenced argument'. Sadly, the determination of penicillin's structure did not lead to cheap chemical synthesis but it was another landmark in chemistry and crystallography. In the volume *Chemistry of penicillin* (8) Dorothy says:

At this time the chemical evidence was in a particularly conflicting condition; strong arguments were quoted against both the  $\beta$ -lactam and oxazolone formulae, and the tricyclic structure had for some time seemed very unlikely on crystallographic grounds. The search for the shape of the molecule in a chemically unbiased way, from the X-ray data alone, was accordingly to some extent forced upon us.

Even after the crystal structure had been solved there was still resistance from chemists. As a final concession to the possibility (unlikely in the extreme) that the ring was a product of X-radiation on the crystal, irradiated penicillin crystals were tested for antibiotic activity and proved to be fully active. This paralleled the earlier experiment on pepsin crystals, when their loss of diffraction was shown to be a lattice effect and not a result of a chemical change induced by X-rays. There was one oversight: the crystal model is the mirror image of the true molecule; Dorothy had forgotten that penicillamine is a D-amino acid. After this enormous crystallographic effort Dorothy performed surprisingly little structural research on  $\beta$ -lactams and antibiotics. Apart from the major paper in the volume *Chemistry of penicillin* (8), in which the war research was collected, she published only five other papers on  $\beta$ -lactam antibiotics.

The study on thioestrepton, another powerful and interesting antibiotic, was undertaken in the 1960s. M. Bodanszky asked Dorothy to determine its structure by X-ray analysis because classical degradation methods on this large and complex molecule had failed to resolve its chemical constitution. The molecule was large (about 110 atoms) but it contained five sulphur atoms. The crystals diffracted poorly for a small molecule, only to *ca.* 1 Å spacing, which greatly compounded the difficulties of using the obvious approach, Patterson methods. Unfortunately, no heavy atoms could be introduced into the crystal. However, some confidence in using limited diffraction data had come from the insulin research and the structure was finally solved by Bryan Anderson and M.A. Viswamitra by using sharpened Patterson superposition methods based on the five sulphur atoms. Like several structures solved at Oxford, this was a tour de force but it was somewhat overshadowed by other successes on molecules of greater chemical or medical importance.

One of Dorothy's failures was gramicidin S, an antibiotic discovered in the Soviet Union. It was a peptide first sequenced by Dick Synge (F.R.S. 1950). He kept in touch with Dorothy on this, and also prepared some covalent derivatives as part of a project to explore new chemical methods that might be applicable to proteins for use in X-ray analysis. Gerhard Schmidt was assigned the problem. He grew a variety of promising crystals, but none diffracted well. However, their symmetry suggested that the peptide contained a two-fold axis, and with Boris Vainshstein and Galina Tishchenko working in Moscow it was possible to come up with models of the crystal structure. But in spite of years of effort the structure was not solved until Michael Woolfson (F.R.S. 1984), Eleanor Dodson and Steve Hull succeeded in 1978 with the use of direct methods (Hull *et al.* 1978).

#### *Vitamin B<sub>12</sub>*

Vitamin B<sub>12</sub>, the factor that acts against pernicious anaemia, was discovered in 1926 by Minot and Murphy. Its isolation and purification were undertaken by several pharmaceutical laboratories but were achieved only in 1948. Structural research began in Oxford when Lester

Smith from the Glaxo laboratories brought some beautiful deep red crystals to Mary Porter and Reginald Spiller for optical examination. Although they were very small, Dorothy asked if she could examine them and found that the crystals diffracted well; she was able to give him the molecular mass that very day. Dorothy was immediately interested in taking on its structure determination even though very little was understood about its chemical composition and its size, about 100 atoms, made its analysis an almost hopeless prospect. When later it was realized that cobalt was present, Dorothy knew that the structure could be solved and with John Robertson and Jenny Glusker she had people to work on it.

From the beginning there were technical problems. Dorothy realized that the molecule's size meant that the maps could not be interpreted as projections but would have to be calculated in three dimensions. This major computation issue aside, the approach was simple—to calculate a Patterson map and locate the cobalt ion, which could then be used to phase the electron-density map. At the same time, John White at Princeton University began an independent study with material from the Merck laboratories. Dorothy felt that the problem was large enough for two groups and it was agreed that they should keep in contact and compare results with their own X-ray data (collected with slightly different procedures).

As expected, the cobalt was easily located from the three-dimensional Patterson function, illustrated in figure 4*a*. Around it there was an octahedron of smaller peaks that Dorothy identified as coordinating atoms, one of which she speculated, correctly, to be the cyanide group that had recently been found to be present.

Dorothy suspected that a porphyrin ring was present because of the crystal's pleochroism, and indeed she detected a large planar structure in the Patterson map whose  $x = 0.5$  section (shown in figure 6*a*) is calculated through the cobalt–cobalt vector. This she reasonably thought was a porphyrin ring. It was an inspired interpretation and much more right than wrong. An electron-density map phased from the cobalt ion was to most eyes a totally confusing scatter of peaks; nevertheless, Dorothy was able to locate the benzimidazole and other attached groups. However, it proved impossible to resolve the planar ring around the cobalt satisfactorily (see figure 6*b*). Parallel studies were therefore undertaken on modified molecules. The most important of these was a degradation product, the so-called hexacarboxylic acid. The sulphocyanide and selenocyanide derivatives were also prepared in the hope that they would serve as an isomorphous series; unfortunately, they were not isomorphous but proved useful in confirming the cyanide position. A second modification, dichlorobenzimidazole-substituted B<sub>12</sub>, was analysed in 1954. The electron-density map showed the two chlorines replacing the two methyl groups at exactly the predicted positions, an independent proof of the correctness of the nucleotide position and of their proposed and 'outline' B<sub>12</sub> structure, still a long way from being refined. The derivative was prepared at Glaxo by feeding the microorganism producing the B<sub>12</sub>, a mutant form of *Escherichia coli*, with dichlorobenzimidazole. Incidentally, the success of this experiment led Dorothy to speculate whether heavy atoms could be introduced into proteins in a general way by microbiological techniques. In this she anticipated the selenomethionine and protein engineering techniques that have been so hugely successful in protein crystallography over the past five years.

The hexacarboxylic acid crystal contained only the cobalt-containing planar ring system. It was solved easily by Jenny Glusker and John Robertson and revealed to everyone's great surprise that the ring was not a porphyrin: one of the bridging atoms between the pyrrole rings had been lost. This new structure was called a corrin ring, and when checked against the electron density of the vitamin B<sub>12</sub> it could be seen to fit sensibly. From then on the analysis of the

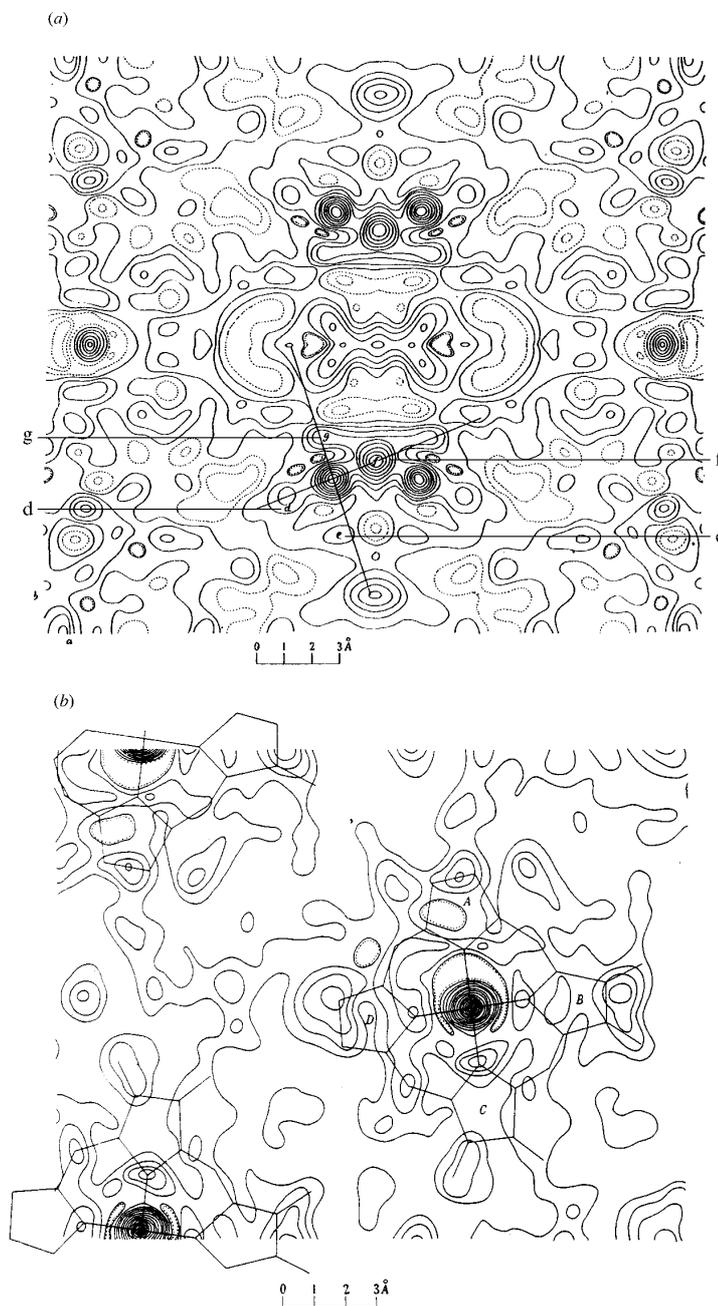


Figure 6. The early steps in determining the structure of the air-dried vitamin B<sub>12</sub> crystal (10). (a) The section at  $z = 0.5$  from the three-dimensional Patterson map for an air-dried vitamin B<sub>12</sub> crystal. The four strong symmetry-related peaks indicate cobalt-to-cobalt vectors. The peaks lettered d, e, f and g represent atoms coordinating directly to the cobalt; the peak d was postulated to represent cyanide. The two lines show the orientation of the molecular feature (the corrin ring) responsible for the crystal's pleochroism. (b) The first electron-density map ( $\rho_1$ ) from the air-dried vitamin B<sub>12</sub> crystal around the cobalt. The positions of the four pyrrole rings of the presumed porphyrin ring have been placed into this density; they are labelled A, B, C and D. (Figs 1 and 5, respectively, from Hodgkin *et al.* (1957).)

vitamin B<sub>12</sub> proceeded from the corrin ring atom by atom. There were no chemical formulae to rely on and every atom had to be selected only on the basis of its appearance in the map and its local contacts. The fear was that they were 'just inventing a molecule'. It was in this phase that Dorothy's crystallographic and chemical judgement was decisive. After a series of ups with the success of Ken Trueblood's computing and the B<sub>12</sub>SeCN maps, and downs caused by mistakes and endless worries about their interpretations of the maps, the full B<sub>12</sub> structure was finally achieved just in time for the IUCr Congress in Paris in 1954.

The announcement of the vitamin B<sub>12</sub> structure had an enormous impact: Bragg described it as 'breaking the sound barrier'. Dorothy knew what had been accomplished. However, she was concerned that the chemists should understand the significance of their stunning accomplishment—the complexity of the vitamin B<sub>12</sub> molecule had put it beyond the capacity of chemical analysis and the classical approaches of degradation and synthesis. Moreover, the crystal structure provided a basis for new synthetic approaches. A.J. Eschenmoser (For.Mem.R.S. 1986) in particular regarded the corrin ring with its nine chiral centres as 'the finest gift that X-ray analysis has so far bestowed on the organic chemistry of low molecular weight natural products' (Eschenmoser 1963). It was now clear that X-ray analysis was the most effective tool for determining structure, with the added advantage that stereochemical features such as chirality, bond geometry and ligand–solvent interactions came as part of the answer (Dunitz 1981). There were some tensions with Todd, whom Dorothy considered to be reluctant to recognize the nature of their achievement. Consequently Dorothy, or members from her group, attended the meetings about the vitamin to put an end to the question she was too often asked: did she believe Todd's structure?

In 1960 Barker and his colleagues (Barker *et al.* 1960) described the isolation of the vitamin B<sub>12</sub> coenzyme, essential in the action of several bacterial enzymes that act to bring about a hydrogen shift between adjacent atoms. The coenzyme contains an additional nucleotide, 5-deoxyadenosyl, coordinated to the cobalt and replacing the cyanide. When in 1961 the determination of its crystal structure was undertaken by Galen Lenhert and Dorothy it was readily solved. Most unexpectedly, the nucleotide was found to have replaced the cyanide by coordinating to the cobalt through the 5' CH<sub>2</sub> of the ribose, losing its hydroxyl group in the process. This raised immediate questions. R.J.P. (Bob) Williams (F.R.S. 1972) in Oxford warned her that the structure must be wrong, that it had the character of a Grignard reagent and should be very unstable in water. His advice was not to publish it, remarking that this was a bad time to ruin her reputation. However, after several days Dorothy informed Bob 'it's still there'. She knew that the structure was right. The explanation for the coenzyme's stability lay partly with the surrounding fence of amides and was also a consequence of slow reaction kinetics caused by the trivalent state of the cobalt in the coenzyme.

Dorothy was very interested in B<sub>12</sub> chemistry and structure and she continued to study B<sub>12</sub>-related molecules leading to a further 20 or so papers on modified species and on careful analysis of the conformational character of the corrin nucleus. Of particular interest was the use of neutron diffraction to determine the H atoms; this finally made it possible to characterize the conformational behaviour of the circle of amide and acid side chains on the corrin ring, which protected the cobalt–carbon bond. This research also led to some very detailed examinations of the water molecules, their hydrogen bonding and interactions.

*Small-molecule crystal structures*

Although Dorothy is known for her major discoveries on the steroids, penicillin, vitamin B<sub>12</sub> and insulin, she investigated many other molecules that were interesting from a medical or crystallographic point of view or that addressed some chemical or biochemical question. In many cases these came to her laboratory from Oxford or abroad simply because of her reputation. These structures broadened the intellectual environment and provided excellent problems for students and visitors. An example is morphine, whose crystal structure was solved in 1955 by Maureen Mackay from Australia. Some of the analyses became minor epics. One such molecule was ferroverdin, undertaken by Sophia Candeloro from Italy. It was an interesting, green, iron-containing pigment extracted from *Streptomyces* by Ernst Chain. Like insulin it had two crystal forms, rhombohedral and monoclinic, and contained a metal atom. Dorothy's last crystallographic paper describes the re-examination of the so-called Piloty compounds; typically, one of the authors is Chinese.

*Insulin and proteins: early days, 1935–59*

One day in 1934, not very long after arriving from Cambridge, Dorothy was given a sample of microcrystalline insulin by Robert Robinson. She was already conversant with the hormone's medical importance and had already worked on protein crystals, so she was immediately interested. This encounter changed her research plans completely and led to a 34-year journey to its solution. When she examined the preparation she saw with excitement that it contained colourless rhombohedral crystals that were, however, far too small to photograph. Following the recipes of Abel and Scott she grew larger crystals by cooling solutions down over several days from 60 °C to room temperature in a large Thermos flask, a technique that was used for many years. After refining her procedures she obtained crystals of a suitable size, albeit ill-formed and flower-shaped. To prepare these for photography Dorothy first filtered them, washed them in methanol and then dried them, not good practice with protein crystals—but in contrast with pepsin these crystals when dry were still birefringent and, she assumed, ordered. And indeed the crystals diffracted. After a 10 h exposure she saw 'the central pattern of minute reflections' and experienced 'probably the most exciting moment' of her life. She told the story many times of her wandering around Oxford late at night in a state of euphoria, then panicking in the morning when she doubted whether the crystals were protein and rushed back to the laboratory to do 'a Xantho protein test'.

Her analysis of the air-dried insulin crystal was similar to the earlier examinations of crystals that she had done with Bernal while in Cambridge. The cell dimensions and symmetry suggested the insulin molecule's molecular mass to be 37 200 Da, near to the 35 100 Da found by Svedberg in his ultracentrifuge studies. The three-fold symmetry in the crystal meant that the molecular mass could be one-third or one-sixth of 37 200 Da, both values being compatible with a smaller, aggregating, molecule of either the 12 000 or 6000 Da proposed by K.J. Freudenberg (For.Mem.R.S. 1963). The existence of an insulin monomer of molecular mass 6000 Da was finally established when Fred Sanger (F.R.S. 1954) determined the hormone's amino acid sequence in the 1950s.

The decision to mount an air-dried crystal for study was perhaps a mistake, but fortunately rhombohedral insulin crystals are robust: they diffracted to *ca.* 6 Å spacing and there was no evidence of radiation damage. Thus there were advantages in working with air-dried crystals and the quantity of data was conveniently small, about 260 reflections. A full three-dimensional dataset was collected and measured, followed by a set from the wet crystals—a much

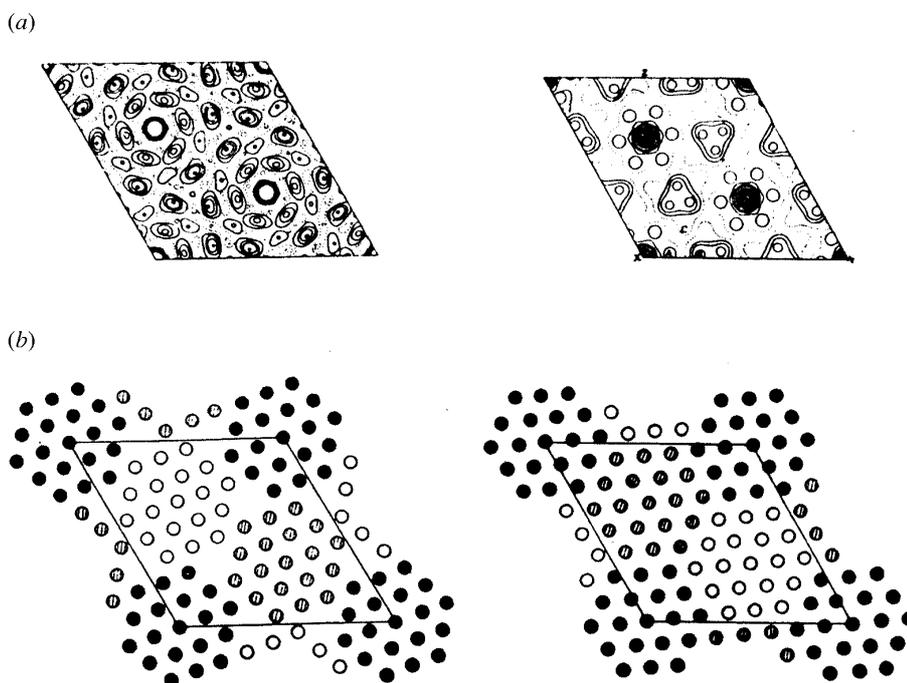


Figure 7. The structural relationship between wet and dry 2Zn insulin crystals (6). (a) The 2Zn insulin Patterson *hkiO* projections for wet (left) and dry (right) crystals. (b) The arrangement for points related to the features in the Patterson map is shown for the wet and dry rhombohedral insulin crystals. Note that there is a similar pattern of hexagonal features in the wet and dry Patterson maps; however, they have undergone relative rotations. This was interpreted as evidence for the protein molecules' changing their relative orientations but not their structures in the wet and dry lattices. (Reprinted with permission from *Nature* (vol. 144, pp. 1011–1012). Copyright 2002 Macmillan Magazines Ltd.)

longer process. These data made it possible to do calculations following the ideas of A.L. Patterson, who in 1934 had shown that a Fourier series summing the diffraction intensities with zero phase produced a function whose peaks represented vectors between all pairs of the atoms in the cell. There were about 2400 protein atoms in the insulin crystal cell and there was no conceivable hope that any structural information could be extracted. Dorothy's observation was that the situation was 'impossibly complex'. Even so she went ahead and calculated the Patterson functions, fully realizing that she would not see unique vectors in the Patterson maps that would define insulin's structure but curious about their features (5). These calculations were enormous and stretched into the war years. The same calculations were repeated with data from wet crystals and later on the wet and dry lactoglobulin series with Dennis Riley. Dorothy's curiosity was justified (6). As figure 7 reveals, a comparison of the wet and dry Patterson maps showed that the pattern of intramolecular vectors, generally close to the origin, was essentially unchanged on drying although their orientation had altered. In contrast, the intermolecular vectors, generally further from the origin, showed differences implying that on drying the structure of the protein molecules was not affected but their packing in the lattice was. These observations were fundamental—they provided the first direct evidence that insulin and lactoglobulin, and presumably other globular proteins, had a conserved three-dimensional structure independent of their crystalline or solution states.

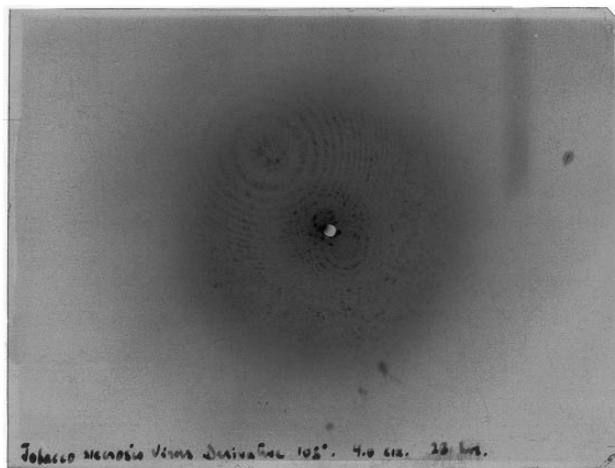


Figure 8. A stationary X-ray photograph of the tobacco necrosis virus derivative crystal taken at the Royal Institution in London. The crystal was irradiated for 23 hours in this exposure. The X-ray reflections extended to 2.8 Å spacing.

As soon as Dorothy had established the crystal cell dimensions and had some idea of insulin's molecular mass and the zinc stoichiometry, she wrote to Bernal about her findings. In his amazing reply he pointed out that there was likely to be an isomorphous series with zinc and other divalent metal ions; especially he noted cadmium with its extra 20 electrons (15). This was therefore the first opportunity to determine protein phases experimentally and Bernal saw it immediately. Unfortunately, but not surprisingly, Dorothy was unable to grow sufficiently large crystals of cadmium insulin; the material was always more difficult to crystallize than zinc insulin and needed much higher purity than was then available. However, cadmium insulin came into its own in 1971, when it was used to extend the experimental phases of the 2Zn insulin series to 1.9 Å from 2.8 Å. Another attempt to add heavy atoms was based on chemistry: Dr Reiner and Dr Lang at the Burroughs–Wellcome Laboratory in the USA sent very small yellow crystals of insulin linked to iodobenzene. However, the diffraction patterns were very weak and no more material was available to grow bigger crystals.

From Oxford Dorothy kept in close touch with the Cambridge laboratory. She was well aware of the studies there on other proteins, including the tobacco mosaic virus, being investigated by Fankuchen, and the tobacco necrosis virus (TNV) crystals, grown by N.W. Pirie, F.R.S., and studied towards the end of the war by Gerhard Schmidt. TNV is referred to as a derivative because after its preparation for crystallization it was no longer infective. The crystals were large (1–5 mm) and diffracted so well that it was possible to record the data to 2.8 Å. The first diffraction pattern was recorded unintentionally with a stationary crystal; Gerhard had forgotten to turn on the camera's motor. Its pattern of intersecting circles (see figure 8), was a surprise and it took a little time for them to realize that this phenomenon was a consequence of very long axial lengths of more than 300 Å. Further 2.5° oscillation photographs were taken and the diffraction pattern was analysed in detail. The dimensions of this approximately spherical molecule and its molecular mass (1 850 000 Da) were estimated and its space group, triclinic *C1* or pseudo-monoclinic *A1*, deduced. Its crystal dimensions are similar to those of the monoclinic form obtained later for the virus by Aaron (later Sir Aaron) Klug (F.R.S.; P.R.S. 1995–2000) and his colleagues. This remarkable study showed that molecular

entities of the size and complexity of virus particles were accessible to X-ray analysis: all that one needed was crystals (7).

Initial studies were performed on other proteins that came Dorothy's way. These included ferritin, given to Pauline Harrison and solved in Sheffield, and lactoglobulin, studied by Dennis Riley and solved much later in Leeds. She generally passed such proteins on to others so as not to be deflected from insulin.

*Insulin research: the later years*

After the war, Dorothy's research into insulin was displaced by the studies on penicillin and on vitamin B<sub>12</sub>. However, it is clear from her writings that she continued to think about methods to attack the structure of insulin and she was acutely aware of the research in Cambridge where Max Perutz and John Kendrew were already having success with heavy-atom derivatives (see p. 193). Dorothy herself had long experience in using heavy atoms to phase cholesterol, penicillin and vitamin B<sub>12</sub> and was ready to return to insulin. It was, however, only in 1959 when Marjorie Harding joined Dorothy for her doctorate that she returned to insulin research as her main interest.

Marjorie started her research on the 2Zn crystals she had already studied, and on a new form, the so-called 4Zn insulin, discovered by Dr Jorgen Schlichtkrull at the Novo Terapeutisk Laboratories in Copenhagen. Both of these crystals were rhombohedral, which meant that there were no centric zones to simplify crystallographic calculations. In addition there were no obvious chemical groups in the protein to react with heavy atoms. Systematic experiments in which the insulin crystals were soaked in an enormous range of heavy-atom solutions produced very few candidate derivatives, none of which proved useful. Only one of these suggested encouraging substitution, a mercury iodide complex in the 4Zn crystal form that exhibited marked anomalous scattering effects. This was very important because anomalous differences, when combined with the isomorphous differences, first allowed the contribution of the heavy atom to the X-ray reflection to be determined and a proper Patterson function for the heavy-atom series to be calculated. It also provided extra information for deriving phases. In the middle of these promising developments Sivaraj Ramaseshan arrived from Bangalore. He was an experienced crystallographer who had done original work on anomalous scattering and was able to contribute both theoretically and experimentally to the insulin research. In addition he planned to investigate the use of these methods with neutrons, complementing the X-ray studies. Dorothy told me that at her suggestion Sivaraj discussed this attractive idea with Bernal, who, after a calculation, said that the existing slow-neutron sources lacked the necessary intensity to be useful, which indeed turned out to be so.

Research continued on both 2Zn and 4Zn forms. Disappointingly, the heavy-atom sites for the 4Zn insulin HgI<sub>4</sub> derivative could not be found. The X-ray data and the anomalous effects seemed so excellent that this failure deeply puzzled Dorothy, but for Marjorie Harding it was an awful blow. We now know that it was not because of deficiencies in the mathematical formalism or the X-ray measurements but the very complex pattern of substitutions spread over a great many sites that introduced large but undetected non-isomorphous effects. This failure led to research on other insulin forms such as the monoclinic and protamine-containing crystals (the latter widely used in diabetes therapy). But all these studies foundered owing either to the fragility of the crystals or to the difficulties in introducing ordered heavy atoms.

Thus, research concentrated on the strongly diffracting, robust, rhombohedral 2Zn insulin crystals. The analysis was tackled by a group whose composition inevitably changed over the

years. Throughout, Dorothy provided an essential stimulus, a source of ideas and confidence that the problems would be solved. The first real breakthrough came when, following Bror Strandberg and Tillander's advice to Dorothy, we found that the zinc could be removed from the crystals and lead atoms introduced without damaging the crystal too much. This was a difficult experiment and only successful after many frustrating trials in which the crystals usually shattered. Once achieved, however, we found to our surprise that the pattern of substitution was complex. The zinc sites on the three-fold axis were occupied as expected, but there were also sites at the centre and the perimeter of the hexamer whose occupancy, very sensitive to pH, easily damaged the lattice and reduced the quality of the diffraction. However, the phases derived from this and related derivatives were just not accurate enough to produce an interpretable map. There were several other developments that were critical for success. These included the preparation by Tom (later Sir Thomas) Blundell (F.R.S. 1984) of a series of uranyl derivatives and the characterization of the zinc-free insulin crystals by Margaret Adams, the refinement calculations of Eleanor Dodson and M. Vijayan, and the optimization of data collection procedures by Ted Baker on the new four-circle diffractometer, which was capable of much more accurate measurements. In the end, five heavy-atom derivatives were prepared. Each of these derivatives was imperfect because of disorder or non-isomorphous effects. We were additionally nervous about progress when we compared them with the lysozyme derivatives and realized that the best heavy-atom derivative of insulin was less promising than the worst from the lysozyme series. However, when their contributions to the phases were combined they gave some very encouraging indications. Dorothy, sensing that success was now close, gave continuous and enthusiastic support, ready with advice and ideas. The map was calculated with data extending to 2.8 Å spacing, which was not as high as we wished. After an initial and frightful anxiety arising from a hasty too-close stacking of the map sections, it was fairly easily interpreted over three happy days by Dorothy, Vijayan and myself, Tom being unwisely away in the USA on holiday before going on to the IUCr Congress in Buffalo. It was a triumphant occasion in which Dorothy, although suffering from swelling ankles and forced into wearing slippers, worked with concentration and wonderful spirits. Everything fell into place. Questions that had been puzzled over for years were answered: the nature of the structural differences of the two chemically identical insulin molecules in the crystal's asymmetric unit; the geometry of the local symmetry that was exactly as predicted by Michael Rossmann (For.Mem.R.S. 1996), David Blow (F.R.S. 1972) and Eleanor; the pattern of assembly of the monomers to dimers and the dimers to hexamers; the symmetrical octahedral zinc coordination and its role in the hexamer formation; the nature of the sequence variation between species. The structure also confirmed Sanger's disulphide bond pairings, something that to our great surprise he admitted having worried about.

All this happened just two weeks before the IUCr congress in Brookhaven. It is characteristic of Dorothy that she insisted that Tom, down to speak on 'progress towards solution', should nevertheless give the first presentation of the structure, the culmination of 35 years of her research. There was an insane scramble to get figures drawn and slides made in time for him to present the structure, very successfully. This first very rushed approach to analysing insulin's structure and biology was followed by much more considered thinking. It led to an almost complete understanding of the hormone's behaviour in solution, the basis of its chemical reactions, the rationalizing of the molecule's folding properties and their dependence on disulphide bond formation. The dimer and hexamer arrangements led to a detailed understanding of insulin's self-association, accounting for its solution behaviour and many of its

spectroscopic properties (13). In the words of Don Steiner, who discovered insulin's biosynthetic precursor proinsulin, the crystal structure 'provided an intense stimulus in a field that had begun to wither'. The clinical benefits were slower but the three-dimensional structure led to the design of genetically modified monomeric insulins that have significantly improved diabetes therapy. In addition, the crystal structure identified the surfaces that were involved in the hormone's biosynthesis and it provided a framework for investigating receptor binding.

The determination of insulin's structure was performed with data limited to 2.8 Å spacing. For Dorothy, one logical step as a crystallographer and chemist was to complete the analysis by extending the data. John Cutfield, another New Zealander, joined in this exercise. The extension of the data began first to 1.9 Å with experimental phases (incorporating cadmium and lead insulin), as Bernal had suggested in 1935. This exercise was followed by extending the data to 1.5 Å spacing and refining the atomic parameters by normal crystallographic methods. Lyle Jensen had set a precedent for these calculations by refining another small protein, rubredoxin, at this resolution. The main difficulty faced in this exercise was handling the mass of data, and here Dorothy's crystallographic and chemical skills, allied to her memory and capacity for organization, and her characteristic refusal to be discouraged by complexities, proved invaluable. At the same time, unknown to us until 1971, the Chinese crystallographic group in Beijing had also determined the 2Zn insulin structure with the use of different derivatives. Their first map was calculated early in 1970 with 2.5 Å data, followed by a 1.8 Å map a few years later. The experimental phases were obtained from beautifully isomorphous derivatives and were impressively accurate. These studies in China and in Oxford revealed structures that were identical within the limits of error, giving Dorothy enormous satisfaction. Because the crystals studied were the same, the identical results completely confirmed the validity of the crystallographic methods that we were using. And of course the emergence of an effective protein crystallographic research group in China showed that developing countries could also make a contribution to the field.

The high-resolution insulin data were also an opportunity to investigate how to apply to proteins the direct methods of structure determination that were so powerful when applied to small molecules. David Sayre, with Neil Isaacs at IBM, wanted to use the 1.5 Å data in experimental calculations. Dorothy, although unsure of the outcome, was enthusiastic. Others were involved, namely Janos Kirz from Brookhaven, John Cutfield and Eleanor Dodson. There were some enormous calculations both at IBM and on the Atlas computer at the Rutherford Laboratory. The calculations revealed that 1.5 Å data were not quite sufficient for robust results: although well-defined atoms usually appeared as resolved peaks, less well-defined atoms behaved unpredictably—sometimes they were present overweighted, sometimes absent. The experiments were a beginning for the phase determination procedures that are now proving effective with data extending to less than 1.2 Å spacing. Experiments were also begun by George Tsoucaris and Collette de Rango from Paris, using the determinantal methods that they had developed. There was also contact with Nori and Kiwako Sakabe from Japan, who had visited Dorothy in the 1970s and who were continuing their own refinement work on insulin. They later collected data from 2Zn insulin crystals on the Japanese synchrotron. This extended out to 1 Å spacing, allowing them to locate H atoms.

The more conventional refinement calculations themselves stretched over 14 years, beginning in 1974 when the collection of 1.5 Å data was completed. Several new ideas were applied in this exercise, including restrained refinement and fast-Fourier block-diagonal least-squares minimization, developed with Eleanor Dodson, John Rollett, Neil Isaacs and R. Agawarl. The



insulins prepared by Helmut Zahn and Dietrich Brandenburg and their colleagues at the Wollforschung Institute at Aachen, and the hagfish insulin obtained through Stur Falkmer and Stefan Emdin at Umeå. These insulins, which were studied by John and Sue Cutfield, had a very low potency and their analysis provided important evidence concerning the hormone's active surfaces. The analysis of the other rhombohedral insulin, the 4Zn insulin form, was begun in the early 1970s. It could not be solved by simply exploiting the 2Zn insulin crystal as we expected, and the phases had to be determined experimentally. The structure was completed by Graeme Bentley and Dan Mercola in 1976, the year before Dorothy retired, and provided her with an example of the unpredictable nature of the structural properties of proteins (14). The 4Zn insulin structure bore a close relationship to the 2Zn form, but there were very surprising differences. The position and extent of the symmetry of the local two-fold axis had changed, there were differences in the Zn coordination and a conformational movement that switched the B-chain N-terminus from an extended strand to a helix. This explained why its solution was not achieved by using the knowledge of 2Zn insulin. Extraordinarily, this transformation of 2Zn to 4Zn insulin moves the N-terminal residue by 30 Å, yet it occurs in the crystal without it shattering. Here was an unexpected message about insulin's flexibility that forced us to think more about the relationship between protein sequence and structure.

There were some satisfying consequences for diabetes therapy from the analysis of the rhombohedral 4Zn insulin crystal. It was used extensively in treatment because, combined with zinc, it formed a relatively insoluble crystal with protracted action, the so-called 'lente-insulin' developed by Novo Laboratories in Copenhagen. The structure revealed why this prolongation of action occurred. The new conformation of the N-terminal segment, B1–B8, covered the zinc site and greatly decreased its exchange with the solution, thus stabilizing the hexamer and decreasing the rate of its breakdown into soluble monomers. Interestingly, an essential step in the successful clinical use of monomeric insulins in the 1990s also depended on understanding how to exploit this structural behaviour in the hexamer.

Insulin was obviously one of Dorothy's most important commitments, but the small number of early publications reflects the limited possibilities for this research. Before the war, just four papers were published; the next, written in 1966 with Marjorie Harding, was the second part of the long 1938 paper, giving a detailed report on the X-ray patterns and Patterson functions of the 2Zn and 4Zn rhombohedral crystals. Another substantial paper followed, also in 1966, describing the results of the molecular replacement calculations with Michael Rossmann and David Blow. The paper in 1969 describing the crystal structure was the tenth publication on the hormone, but over the following 14 years 38 papers were published covering the hormone's structure, biochemistry and biological behaviour.

## SCIENCE AND SOCIETY

### *University*

In 1970 Dorothy became the Chancellor at Bristol University. There are Chancellors and Chancellors. Dorothy took the position seriously and willingly accepted many of its more or less voluntary aspects. It was a remarkably open and friendly regime in which Dorothy's interest in the whole university was evident. There was a particularly close sympathy between her and the Vice-Chancellor, Sir Alec Merrison, F.R.S., and she also had an obvious interest in the students. When in Bristol on official visits she took time to mix with them and to discuss the

university issues and other issues that affected them; although unusual in a Chancellor, it was natural for Dorothy.

At about the same time, Dorothy also joined a Review Body, chaired by Jo Grimond, with the remit to examine the constitution of the University of Birmingham and to make recommendations that reflected the changes occurring in academic life and society. There were several important issues in this exercise, which included the increasing financial pressures and their impact on university decisions, the need to increase the participation of all staff and of students in university affairs, and the very low proportion of women students in university going on to teaching and research. There was an immense amount of paperwork; her response on receiving one huge packet of documents was to reply simply, 'I will read them—gradually'.

There were many happy occasions for Dorothy at Bristol. The establishment of Hodgkin House for overseas and especially African students, in memory of Thomas and his African connections, was especially important to her; it reflected the outward and generous instincts at Bristol that so warmed her to the university and the city. Dorothy believed profoundly in the importance of education and that it should be available to all. A reflection of this conviction was her willingness to travel to schools of all kinds, large and small, as well as to distinguished centres of learning and research. There is also no doubt that Dorothy got real pleasure from these visits even though they were often onerous, time consuming and distracting. Many have remarked how at these occasions Dorothy put her hosts at ease and communicated her interest, usually very informed, in the teaching and research going on. She always wanted to talk to the students and her friendly approach and obvious interest in their doings removed the barriers that often exist between the famous and their audiences. Max Perutz has recalled, 'Dorothy's interest in students was remarkable, she insisted on mingling with them and on occasion ate with them' (letter to the author, May 2001). Sir John Meurig Thomas, F.R.S., recalls a trip by Dorothy in 1970 to the University of Aberystwyth, which captures the character of such visits. First she was not deterred by the distance and time involved, readily agreeing to come. After the long drive from Oxford, which she enjoyed for its scenery, particularly the view of Cardigan Bay in the afternoon sun, she gave a 'riveting' account of her researches into insulin's structure and function to a large and general audience. And both before and after the lecture she mingled happily with the students, the staff and the visitors who had come to hear her talk. She always enjoyed the graduation ceremonies and put serious efforts into her speeches. They addressed especially such issues as education cuts and their consequences for British education and for average and poor families. She referred often to the disparity in spending on higher education and research in the UK and other advanced countries. She spoke most forcefully about what this meant for individuals living through the problems presented by accelerating technological and social changes. There is no doubt that she would have greatly approved of the more recent expansions in student numbers but would have been alarmed by the immense increases in scientific investment in the USA and its failure to be matched in the UK and in continental Europe. In her last address in 1988 she spoke to the students with her usual directness. She reviewed the prospects for careers in a materialistic and wealthy society and remarked that she hoped that 'some would live modestly and do serious things'.

In 1982 Bristol University's income was severely reduced by government cuts. After much heart searching the decision was made not to spread cuts evenly but to concentrate them. This, among other contractions, led to the proposal to close the Department of Architecture. Dorothy did not agree with this decision; the department was small but excellent, and its involvement

in city and community affairs was very important for the university. It was an uncompromisingly fought issue. She, like many, found it difficult to accept that financial pressures should dictate such decisions; other solutions to maintain the viability of the Architecture Department should be found. Dorothy felt that as Chancellor she should represent her views but knew that these opposed those of the university's senior management. Dorothy nevertheless spoke against closure but in the end the votes went against her and her supporters. The issue of university financing in the new economic and political climate that had emerged in the Birmingham review had surfaced brutally in Bristol. It was inevitably an exceedingly testing time for the university, but throughout there was a general acceptance on all sides that people's views were honestly held and had to be heard. To some degree Dorothy helped in preserving these attitudes. The outcome, however, was the closure of the department, but the vigorous and widespread support it enjoyed led to the establishment of the Bristol Centre of Advanced Architecture. Dorothy herself was heavily involved in obtaining support for the Centre and played her part in approaching suitably wealthy contacts. She did not wholly enjoy this exercise but was motivated by her sense of responsibility as Chancellor and by the rightness of the cause. There is a letter written during this time that captures some of her feelings over fundraising. In this she quotes from the ironic poem 'Dipsychus' by Arthur Clough about the benefits of having money:

As I sat in the cafe I said to myself  
 They may talk as they please about what they call pelf,  
 They may sneer as they like about eating—drinking  
 But help it I cannot, I cannot help thinking  
 How pleasant it is to have money heigh-ho  
 How pleasant it is to have money heigh-ho

I sit at my table 'en grand seigneur'  
 And when I have done throw a crust to the poor,  
 Not only the pleasure itself of good living  
 But also the pleasure of now and then giving  
 How pleasant it is to have money heigh-ho  
 How pleasant it is to have money heigh-ho.

Dorothy retired as Chancellor in 1988 after 18 years, a much loved and admired figure.

#### *Society and science*

Dorothy's belief in social justice and her uncompromising hatred of militarism were, I believe, part of her. In part, of course, it came from her mother, whose natural humanity was perhaps given this direction by the loss of all her brothers in World War I. When visiting the Sudan as a child, and Palestine before going to Oxford, she also saw for herself the nature of colonial tensions and oppression. The time in Cambridge with Bernal and other like-minded people brought Dorothy into contact with the political issues of the day, while the Spanish civil war brought home the seriousness of the Fascist threat posed by Hitler and Mussolini. These events drew Dorothy, like many others, to the belief that the Soviet Union's commitment to socialist principles made it a natural ally. After the war, the anti-communist attitudes helped confirm the need to maintain contact with the Soviet Union and other socialist states. As the nature and extent of Stalin's excesses emerged she still remained committed to her friends; the need to build contacts with them was strengthened by the problems that they faced.

After the war, Dorothy became a prominent figure in the debates on nuclear weapons, dis-

armament and in the various political and military conflicts around the world. Her own strongly held political convictions were socialist but these did not interfere with friendships or discussions with others with utterly different views. She once said to me in a scientific context, but clearly thinking in general terms, that having enemies was a waste of time and energy; this was better spent in avoiding making them. Dorothy's approach to the problems in international issues was the same as that which characterized her research. It was based on an essential sympathy for people, a reluctance to condemn them and a belief that the best way to find solutions was through discussion. In the end she felt that one simply had to assume that people were honest and meant well. Thus, political issues were translated into a personal dimension and the abstractions of political theory and the realpolitik were avoided, which made her arguments difficult to counter. This approach certainly made her laboratory a friendly and productive place, and in the larger and more formal international arenas it often proved to be effective, but when faced with the fear and paranoia generated by ideology and ethnic hatred this essential trust could fail.

Dorothy's approach made her open to the charges of naivety in political matters, instanced by her willingness to talk to individuals, whatever their history or associations, and by her reluctance to criticize communist states publicly. Three visits to the USA after the war widened her knowledge of its crystallography and science and American attitudes. However, her left-wing political associations barred her from the USA between 1953 and 1957, adding to her reservations about American political policies and her anxiety about the growing East–West tensions. However, the refusal of an American visa made it possible for her to go on a delegation with Bernal to the Soviet Union. This was a visit she very much wanted to make—it enabled her to see for herself the state of science and society there—and brought her into contact with the Soviet scientists whose numbers and activity impressed her. The visit instigated a number of friendships and various long-term collaborations such as those on gramicidin S, which she had studied with Gerhard Schmidt in 1945.

At the time of this first visit Dorothy already knew something of Stalin's enormities and about the arrest and disappearance of Western visitors and Russian scientists, although she still remained suspicious of Western propaganda, memories of which went back to World War I. She also had an unshakeable belief in the benefits of socialism and felt she should support socialist and communist governments. Particularly during her first visit to the Soviet Union, Dorothy was enormously impressed by the enthusiasm and idealism that she saw in individuals as well as the practical steps for education, science and technology in the plans for reconstruction. This experience and the quality of many of the scientists and intellectuals that she met confirmed her hopes for the communist system. When she saw the affection and respect that the Russians had for Bernal and his ideas, she could understand his enthusiasm for the communist system and could believe he had influence. On this first visit to Russia, however, she had to decide how best to confront the political abuse and persecution going on there. She had been asked to enquire into the whereabouts of a 'long list' of missing people. Bernal's advice was sought because he could make enquiries at a high level. Dorothy was deeply anxious about the fate of these people but she felt powerless to do more, and just remained generally hopeful that good sense would prevail.

As she became more famous and particularly after she got the Nobel Prize, there was an increasing number of requests to sign petitions or for help in getting people, often dissident scientists, to be released from imprisonment and maltreatment in the USSR and other countries. Because these requests often came from friends she felt profoundly torn. On the one

hand she recognized the need to help; on the other she felt that signing petitions or taking a public stance was, rightly or wrongly, interpreted as propaganda and ineffective. She consulted Thomas and especially Bernal, who had inside knowledge of the Soviet Union. Their advice was the same: in these matters it was best to maintain friendly and trusting contacts with the Soviet scientists, which meant it was important not to be seen publicly condemning Soviet actions. All she could do in response to appeals for support was therefore to write personal letters to her scientific and other contacts in the Soviet Union, and where needed to other countries too. There were many such letters.

In these matters, and in her letters, Dorothy, as was her practice, did not engage much in political argument. In many ways she was not a political person, preferring to keep to specific issues, usually involving people. However, her interest and knowledge of the Eastern block was widely appreciated and her role as an intermediary was valued. On one particular occasion Margaret Thatcher (later Baroness Thatcher; F.R.S. 1983), who had been Dorothy's research student, consulted Dorothy on the conditions in Eastern Europe. This discussion, which involved Mrs Thatcher's advisors, was perhaps instrumental in helping to stimulate her visit to Hungary followed by the contacts between the UK government and Mikhail Gorbachev, and later Mrs Thatcher's own meeting with him.

#### *Pugwash*

The end of World War II brought dreadful knowledge of the extent of the hideous suffering on continental Europe, the enormous losses and destruction, and the cataclysmic surprise and horror of the atomic bombs dropped on Japan. All this affected Dorothy deeply, the more so because people that she had known had died or suffered. The Pugwash Conferences on Science and World Affairs were established soon after World War II with the aim of preventing the use of atomic weapons ever again. They involved scientists from almost every country, including the Soviet Union and China, and especially those with direct experience of the war and the building of the atom bomb. Over the years the agenda of the Pugwash Conference broadened and addressed a range of international issues generally involving conflict.

Dorothy had attended the Pugwash meeting in London in 1962 and several others, but the demands of a young family, her research and her concern over the Vietnamese war absorbed her attention. She joined the Medical Aid Foundation for Vietnam and became its Chairman and a little later, in 1970, joined the Swedish-based Commission of Enquiry into US War Crimes in Vietnam. Her visits to North Vietnam in 1971 and in 1974 with Thomas further strengthened her affection for the people and their struggle for unification, and of course she had sympathy for the communist regime's social ideas and aspirations. Thomas incidentally shared her view of Vietnam's political climate—to Dorothy's delight it was his favourite communist country. Her travels to Vietnam had enabled her to write personal and uncompromising accounts in the press of her experiences there and the consequences of the bombing campaign. These articles raised awareness of the war and identified her as a protester, although she doubted whether this in any way affected the military and political leadership in the USA. The American policy of military action she considered had no legitimate basis; it was inhumane, immensely destructive and pointless, and the UK government's support for it shocked her greatly. It is clear that Dorothy's consistent support for the North Vietnamese has been vindicated by much that has since emerged about the history of the conflict.

In 1975 Jo (later Sir Joseph) Rotblat (F.R.S. 1995) and Bernard Feld came to Oxford and asked Dorothy to become President of Pugwash. In many ways she would be an ideal

President. Her knowledge of the communist bloc, where there were signs of change, together with the friends she had there and in developing countries generally, was balanced by the regard and affection she enjoyed in the West. In addition, the Vietnam conflict was now resolved and her experiences in that lengthy and dreadful struggle would obviously be valuable. However, she was reluctant to accept. Thomas's health was now a worry and she was giving a lot of time to research matters and the refinement of the insulin structure. Nevertheless, she was persuaded that Pugwash only needed a 'remote' President. Things did not turn out like that. It was a natural commitment for her and, in spite of her age and the difficulties in travelling, she attended all the conferences and many of the workshops and symposia. After the first year she wrote to Martin Kaplan, 'I find myself, and probably rightly, more drawn in than I meant to'.

One of her continuing concerns was the absence of China from international bodies. Pugwash had had Chinese representation until the breakdown of Chinese–Soviet relations in 1960. Although Dorothy had good contacts with senior Chinese scientists it was not till the 1980s, to her great satisfaction, that a Chinese delegation returned to Pugwash meetings. There were many other problems: the decision to hold the 25th Pugwash meeting in Poland during the political crisis and after the introduction of martial law was one of the more awkward. Many refused to come and Dorothy was involved in considerable correspondence over the press coverage, generally critical, and some strongly dissenting opinions. In spite of these stressful episodes, the Pugwash practices suited her, based as they were on conversations and discussions by informed serious, and often idealistic, people from all over the world. Dorothy had a natural authority as President, undoubtedly helped by her standing in science. Jo Rotblat describes how she usually intervened very little in discussion, but that when she did her soft voice, and her comments, commanded attention. Most important in both formal and in private discussion she was wonderfully effective in bringing views together. She was President for 13 years, retiring in 1988.

#### THE INTERNATIONAL UNION OF CRYSTALLOGRAPHY (IUCr)

The IUCr was founded in 1946. The idea of the Union was strongly supported by crystallographers all over the world; its formation was a chance to re-establish scientific connections after the war and to accelerate the renewal of research. Dorothy was a keen advocate of the IUCr, seeing its triennial congresses held throughout the world as a forum for scientific and international contact. Dorothy missed very few of these and strongly encouraged members of her own laboratory to attend them. They were sometimes the venue for presenting her most important accomplishments: the vitamin B<sub>12</sub> structure in Paris 1954 and insulin at Brookhaven in 1969.

Soon after the IUCr's inception the Cold War and the international tensions made themselves felt. Nevertheless, its international spirit was generally preserved. One of the more important issues for Dorothy was the absence of mainland China, whose political leadership could not countenance any organization that recognized Taiwan as a separate state, as the IUCr did. Dorothy maintained contact with Chinese crystallographers for many years, visiting and sometimes taking advantage of contacts made in the politically neutral Ghana, where she spent a good deal of time with Thomas. As the IUCr President from 1972 to 1975 she was in a position of influence, but she was unable to persuade China to join. It was only after the death of

Mao Zedong and the removal of the 'Gang of Four' that in 1978 a Chinese crystallographic delegation attended the Congress in Warsaw and was admitted to the IUCr.

#### MEDALS AND HONOURS

- 1947 Fellowship of The Royal Society
- 1956 The Royal Society Medal
- 1960 Wolfson Royal Society Professor
- 1964 Nobel Prize for Chemistry
- 1965 Order of Merit
- 1970 Honorary Fellow of the Royal Society of Edinburgh
- 1971 Baly Medal of the Royal College of Physicians
- 1974 The Sir Henry Dale Lecture  
Honorary Fellow of the Royal College of Physicians
- 1976 Copley Medal of The Royal Society
- 1977 Gold Medal of the Royal Society of Medicine  
President of the British Association for the Advancement of Science
- 1978 Longstaff Medal of the Chemical Society
- 1980 Honorary Fellow of the Royal Society of Chemistry
- 1983 Lomonosov Gold Medal of the USSR Academy of Sciences
- 1984 Dimitrov Peace Prize, Bulgaria
- 1987 International Lenin Peace Prize

#### MEMBERSHIP OF FOREIGN ACADEMIES

- Foreign Honorary Member of the American Academy of Arts and Sciences
- The Akademi Leopoldina
- Foreign Member of the USSR Academy of Sciences
- Corresponding Member of the Bavarian Academy of Sciences
- Honorary Fellow of the Royal Australian Chemical Institute
- The Netherlands Academy of Science
- Foreign Associate of the National Academy of Sciences, Washington
- Honorary Fellow of the Ghana Academy of Sciences
- Honorary Fellow of the Bangladesh Physical Society
- Member of the Yugoslav Academy of Sciences and Arts
- Corresponding Member of the Puerto Rico Academy of Arts and Sciences
- Honorary Fellow of the Indian Academy of Sciences
- Honorary Member of the Royal Irish Academy
- Member of the Norwegian Academy of Science and Letters

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Dorothy has written an incomplete account of her personal life; some of this has been edited by Katherine Hodgkin and is included in her collected works. Quotations in the text generally refer to this. There are also several recollections about Dorothy's research by former colleagues published in her Festschrift. The interviews recorded for the Royal College of Physicians of London and Oxford Brookes University Medical Sciences Video Archive and the Archives of the Biochemical Society, and the excellent biography by Georgina Ferry, are valuable sources on her life. I have benefited enormously from recollections sent by many who knew Dorothy and I have had helpful discussions with many of Dorothy's friends and colleagues. I have had particular help from Georgina Ferry, Jo Rotblat, F.R.S., the late David Phillips, F.R.S., the late Max Perutz, F.R.S., Siv Ramaseshan and from my wife, Eleanor. And I am most grateful for the discussions with Dorothy's children Luke and Elizabeth, who also provided illustrative material, some of which is reproduced in this memoir. The expert and willing help provided on many occasions by Colin Harris of the Bodleian Library; Caroline Myers at the University of York; Rosemary Sumray, the Library and particularly the Photographic Unit at the NIMR; and David Montagu at The Royal Society are acknowledged with gratitude: their help has made writing this memoir possible.

The frontispiece photograph was taken by The Associated Press Ltd in 1965 on the occasion of Dorothy's appointment to the Order of Merit, and is reproduced with permission. Other than Florence Nightingale, who was appointed O.M. in 1907, Dorothy was the first woman to hold this award.

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