Book Review

The Collected Works of Dorothy Crowfoot Hodgkin. Volumes I, II and III. G. G. Dodson, J. P. Glusker, S. Ramaseshan and K. Venkatesan, eds. Indian Academy of Sciences and Interline Publishing Private Limited, Bangalore, 1994.

Dorothy Crowfoot Hodgkin* is a great scientist and equally great humanist of our times. She is considered to be the greatest structural crystallographer. Her work has profoundly influenced chemistry and structural biology. Her influence on crystallographic research in different parts of the world, through the large number of crystallographers trained with her and through her visits, has been far reaching. She has been deeply involved in the communal activities of scientists in general and crystallographers in particular. Her contributions towards bringing people together and promoting international understanding have been significant. That, however, never prevented her from taking strong positions against oppression and injustice. What endeared Dorothy to her students, colleagues, friends and admirers was not only her science but also her personality. Few have been loved as much as Dorothy has been. She radiated affection and goodwill. What made her so effective in the scientific community and outside is mainly her innate goodness.

A compilation of the papers and articles by a many-splendoured scientist like Dorothy Hodgkin is welcome at any time. The publication of her *Collected Works* in the mid-nineties, when her influence is still vibrant and the memories about her are as yet un-dimmed, is all the more welcome. The *Collected Works*, which has been produced in three volumes, contains her writings spanning more than two thousand pages including a short autobiographical, yet unpublished, account of her early life and career. Furthermore, a common set of articles on her written by her selected colleagues from different parts of the world is given in the beginning of each volume. Volumes I and II also contain introductory articles pertaining to the publications contained in them. Volume I is devoted entirely to papers on insulin, Dorothy's abiding interest throughout her career, while volume II deals with papers on sterols, penicillin and other antibiotics, and vitamin B_{12}. Volume III contains structural papers on other compounds, reviews, historical and biographical writings, general articles and her own short memoirs.

In this review, I have departed to a large extent from the normal practice of dealing with the material volume by volume. The papers published during the formative years of Dorothy's scientific career are discussed first. Her approach to choosing scientific problems and dealing with them, as it emerges from the *Collected Works*, is described next. Then the publications presented in Volumes II, I and III are reviewed, almost in that order.

The first publication of Dorothy Crowfoot is along with H. M. ('Tiny') Powell in the form of a short note in *Nature* in 1932 on the double refraction of thallium di-alkyl halides (Vol. III). This was followed up by the same authors with a detailed paper in 1934 on the crystal structure of dimethyl thallium halides deduced from considerations of space group and unit cell dimensions. These publications resulted from the project work ('Part II') carried out by Dorothy under the supervision of Powell as part of her degree course in chemistry at Oxford. Powell himself was young and new to crystallography and Dorothy was his first student. In most of their subsequent career, they worked in the same laboratory at Oxford (known most of the time as the Laboratory of Chemical Crystallography), headed for a long time by Powell. There is however, no evidence for any further serious influence of Powell on Dorothy's scientific career.

Dorothy's true mentor and the greatest influence on her development as a scientist and public figure, was undoubtedly the legendary J. D. Bernal under whose supervision she obtained her doctorate. Bernal and Crowfoot formed a highly productive combination and they co-authored 10 publications on a variety of problems during 1933–35 (Vols III and II). A couple of them formed the starting point for their subsequent well-known work on cholesterol. They also included the celebrated 1934 *Nature* paper on the X-ray measurements of the crystals of pepsin, the first protein to be so studied, which marked the beginning of protein crystallography. They did not co-author many publications, except for a few on steroids, since then, but Bernal remained a great influence and a source of strength and inspiration in Dorothy's career. Her respect and affection for the 'Sage' clearly comes through in very many of her writings included in the *Collected Works*.

Dorothy returned to Oxford in 1934 to start her independent research career and she remained there ever since. Her first independent publications appeared in 1935. One of them was concerned with the interpretation of Weissenberg photographs (Vol. III) and is perhaps the only paper by her exclusively dealing with methods. As often happens in science, but rarely with Dorothy, she was pipped at the post by Martin J. Buerger who submitted a paper on the same topic to the same journal a little earlier. Dorothy, to her utter disappointment, had to be content with publishing a much truncated version of her original manuscript. Another remarkable and historically very important publication by her in 1935 was her *Nature* paper (Vol. I) on the X-ray measurements on insulin. That marked the beginning of her life-long involvement with the structure of insulin.

Dorothy has solved the structures of a large number of compounds belonging to different chemical families. She kept her eyes and ears open for significant problems, examined most of the interesting ones that came her way and then concentrated on the most important and challenging ones on a long-term basis. Of these, the best known have been cholesterol and related compounds, penicillin and related antibiotics, vitamin B_{12} and related compounds, and insulin. She worked on many systems simultaneously, but her primary concern at any given time appears to have been with one or at best two of these systems. In the second half of the thirties she did a great deal of early pioneering work in protein crystallography, especially on insulin, but the intensity of her work in this area gradually waned, to be revived again to the full only in the sixties. The work on sterols, started along with J. D. Bernal in the thirties, continued into the

*The maiden name Crowfoot was used in most of the early publications while the later publications appear under the surname Hodgkin, acquired after marriage. Most of the time she is referred to by her first name in this review.

sixties, the last paper being one in 1963 on a calciferol derivative. The work on penicillin started around 1940 (much was not published in the early stages of the work on account of the war) and the last paper to emerge from the Oxford group on a compound related to this antibiotic was in 1973 after a gap of five years since the publication of the previous paper in the series. The first paper on vitamin B_{12} appeared in 1950 while the last contemporaneous primary publication came out in 1975. The two 1984 papers on neutron diffraction studies, published in the *Proceedings of the Indian Academy of Sciences*, were concerned substantially with work done much earlier. Active work on insulin in Dorothy's laboratory was revived in the sixties and a paper on X-ray measurements on insulin crystals appeared, after a gap of 27 years, in 1966. The logical completion of this work, and indeed the effective end of Dorothy's illustrious scientific career, was marked by a long publication on the 1.5 Å resolution structure of 2 Zn insulin in 1988 in the *Philosophical Transactions of the Royal Society*. Thus, her four major research programmes were pursued in successive, telescoping stages. While pursuing these programmes, she also worked on several other projects such as, for example, those involving ferroverdin and thiostreptone.

Dorothy's papers on cholesterol, penicillin and vitamin B_{12} amply illustrate the distinctive Hodgkin approach in chemical crystallography and its tremendous impact on chemistry. As mentioned earlier, these papers appear in Vol. II. The introductory material in the volume contains, among other general articles, a retrospective on penicillin by Barbara W. Low and on vitamin B_{12} by Jenny Pickworth Glusker, both former students of Dorothy who worked on the respective problems. To most crystallographers, X-ray analysis involves the determination of the three-dimensional arrangement of atoms in compounds with known chemical structural formula. Not so for Dorothy. She determined the chemical formula itself in addition to the three-dimensional structure exclusively through X-ray analysis. Often, as in the case of vitamin B_{12}, the composition itself was in considerable doubt to start with. Thus, as is often said, Dorothy released organic chemists from the drudgery of structure analysis. In each one of her major programmes, she approached the central problem from different directions. For example, the structure determination of vitamin B_{12} involved the X-ray analysis of several of its derivatives and degradation products. Another characteristic of her approach has been the willingness and the ability to use the latest developments in the field. She was among the first to use the Patterson synthesis in the thirties. She always sought and used the latest machines for computation. For instance, she extensively used the computer facilities at the University of California at Los Angeles for the vitamin B_{12} work through the help of K. N. Trueblood. She was an enthusiastic user of neutron diffraction when it became available. Some interesting neutron diffraction studies were carried out on vitamin B_{12}.

The early papers by Bernal and Crowfoot on sterols and related compounds primarily dealt with preliminary studies on their crystals. They did not involve regular structure analysis as we understand it today. They examined about a 100 crystals very systematically. It is remarkable how very chemically significant results could be obtained from simple, but systematic and intelligent, measurements. These measurements led to a drastic revision of the then prevalent understanding of the chemical structure of sterols and contributed to the development of the correct structural formula. The first detailed analysis of a member of the series was that on cholesteryl iodide carried out by Carlisle and Crowfoot and published in 1945. This analysis firmly established the structure of cholesterol. Since then Dorothy and her colleagues worked out the detailed structures of several sterols and published the results during 1948–63.

Dorothy got interested in the structure of penicillin even as the work on sterols was in progress. The war time efforts to produce large quantities of Fleming's penicillin to protect wounded soldiers from infection, are well known. But less generally known is the brilliant elucidation of the chemical structure of penicillin through X-ray analysis which, among other things, made it possible to synthesize it. Penicillin defied structure elucidation by chemical methods. The β-lactam structure of the antibiotic was established by Dorothy and her colleagues by the middle of the forties through the study of sodium, potassium and rubidium benzylpenicillin. This was among the first studies in which a three dimensional electron density map was calculated, long before it became normal to do so. Unfortunately, this very important piece of work was never published in a proper journal. It was, however, described in detail in an article in the book *Chemistry of Penicillins*, published by Princeton University Press in 1949. The publication of a reprint of this article in the *Collected Works* makes it accessible to a wider range of readers. In subsequent years, Dorothy solved and published important papers on cephalosporin, phenoxymethylpenicillin, ampicillin and a synthetic compound related to penicillins and cephalosporins.

A majority of papers in Vol. II are devoted to vitamin B_{12}, the jewel in the crown. They include primary publications, reviews and transcripts of talks. Almost nothing about its structure was known when Dorothy started working on the vitamin in the late forties. The only worthwhile information that she obtained from chemists soon afterwards is that the molecule contained cobalt. The cobalt ion, located from Patterson maps, was the starting point of the analysis using the heavy atom method. For the large molecule that vitamin B_{12} is, the scattering power of cobalt would be considered by anyone except Dorothy as too small for useful phasing. The challenge becomes all the more formidable when even the structural formula is unknown. In the fifties, Dorothy and her colleagues worked on the wet and dry crystals of vitamin B_{12}, a seleno derivative of the vitamin, a hexacarboxylic acid obtained by the degradation of vitamin B_{12}, a chlorine substituted compound and the B_{12} coenzyme adenosylcobalamin. The structure of the vitamin, compact yet complex, with the novel corrin nucleus, was essentially established by the second half of the fifties. Dorothy went on to work on related vitamin B_{12} compounds for many more years. The work on one such compound, factor V 1A, an investigation in which K. Venkatesan was a key participant, represented the first use of anomalous dispersion in the solution of a large structure.

For sheer intellectual brilliance, there are few crystallographic investigations

which can match the work on vitamin B_{12}. The structure of the vitamin is a monument to Dorothy's unparalleled chemical intuition and crystallographic prowess. She made sense out of the weak density in early Fourier maps, which appeared to be noise to most others. As David Phillips writes in one of the introductory essays, 'she

Turns them into shapes, and gives to airy nothing
A local habitation and a name'.

She brought to bear on the problem all the relevant crystallographic approaches and the latest technology, especially for computation. Most of the problems involved in solving large non-centrosymmetric structures were enumerated and the methods to overcome them were developed in the course of the structure determination of vitamin B_{12}. They became very relevant later to the crystallography of biological macromolecules such as proteins.

Despite her remarkable successes with cholesterol, penicillin and vitamin B_{12}, the problem closest to her heart was insulin. Insulin remained with her throughout her career and, quite appropriately, one whole volume (Vol. I) of the *Collected Works* is devoted to her work on insulin. Again, quite appropriately, the insulin papers are introduced through an article by G. G. Dodson who worked with Dorothy for the longest period and whose length of association with insulin crystals was second only to that of Dorothy's. The first phase of insulin work was part of the 'ancient history of protein X-ray analysis' (recounted by her and Riley in a paper reproduced in Vol. III). This history started when she and her mentor J. D. Bernal recorded and examined the X-ray diffraction pattern from the crystals of pepsin in 1934. Then occurred in 1935 what she reckons as probably the most exciting event in her life, the X-ray photography of insulin crystals. During those very early days of protein crystallography, she worked on other proteins as well, but insulin was the protein that she concentrated on. That was a time when even the exact chemical nature of proteins was unknown. Yet, along with other pioneers like Max Perutz, she persevered. She recorded X-ray diffraction photographs using a primitive oscillation camera, from dry and wet insulin crystals, indexed them and measured the intensities by eye. Then she did what best anyone could do at that time: calculated Patterson maps, a formidable undertaking in pre-computer days, and looked for general patterns. This work was reported in two papers, one in 1938 by herself and the other in 1939 by herself and her student Riley. That is where matters rested for a couple of decades.

Dorothy's next publications on insulin were in 1966, after a gap of 27 years. Much had happened in the meantime. She had solved the structures of cholesterol, penicillin and vitamin B_{12} and earned the fellowship of the Royal Society and the Nobel Prize. Max Perutz and John Kendrew and their colleagues had solved the structures of haemoglobin and myoglobin by the turn of the decade. The crystal structure of an enzyme, lysozyme, had been determined by the group of David Phillips, by then. The structures of several other proteins were well on the way to solution. Thus, protein crystallography, though still in its heroic days, was well established by that time. Also, the amino acid sequence of insulin, determined by Fred Sanger in the fifties, was available by the time the two 1966 papers were published. The first of the two dealt with the two rhombohedral forms of insulin (2 Zn insulin containing 2 zinc ions per insulin hexamer and 4 zinc insulin containing 4 zinc ions per insulin hexamer), cubic insulin and monoclinic insulin. The second paper was concerned with the first application, on 2 Zn insulin and 4 Zn insulin, of the rotation and translation functions developed by Rossmann and Blow, functions which were subsequently to become so very important in the molecular replacement method of structure solution. This work established the internal symmetry (approximately 32 or D_3) of the insulin hexamer.

Since then the work on insulin progressed rapidly and its much awaited structure in the 2 Zn insulin form, at 2.8 Å resolution, appeared in the centenary issue of *Nature* in 1969 to the accompaniment of much celebration. Insulin was, of course, the first protein hormone to be X-ray analysed. The structure, not surprisingly, provided a wealth of information on the polypeptide conformation, intramolecular interactions and oligomerization of insulin. Most of the subsequent publications on insulin in the volume are reviews, abstracts, articles in conference proceedings and transcripts of lectures, interspersed with a few primary publications containing significant new information. The relationship of the structure with every aspect of the chemistry, biology and evolution of insulin has been examined in considerable detail in these publications. An important publication in 1976 reports the structure determination of 4 Zn insulin in which three of the insulin monomers in the hexamer have the same conformation as in 2 Zn insulin while in the other three, parts of the polypeptide chains exhibit a different conformation. This formed the basis of the subsequent detailed studies on the R and T states of insulin. The publications in the volume also give evidence to Dorothy's affectionate and generous involvement with the Chinese and the Japanese work on insulin. The last of her publications on insulin, indeed her last major scientific publication, is a very detailed account of the 1.5 Å resolution structure of 2 Zn insulin which appeared in 1988 in the *Philosophical Transactions of the Royal Society*. That is perhaps the most detailed account of any protein structure published so far. That also marked the culmination of Dorothy's loving, and often passionate, involvement with insulin spanning more than half a century.

Volume III of the *Collected Works* is devoted, as indicated earlier, to her X-ray work on other compounds, general crystallographic articles, essays on different topics, historical and biographical sketches, book reviews, general lectures and unfinished autobiographical memoirs. The mixed character of the contents of the volume makes interesting reading, but makes the job of the reviewer difficult. Her reviews in the second half of thirties, forties and early fifties provide authentic accounts of the contemporary state of structural crystallography. Many papers and articles are concerned with the early days of protein crystallography. Then there are accounts of some splendid structure determinations. Interestingly, perhaps the last structures Dorothy determined, reported in 1982, were those of two simple cyclohexane derivatives. Here is a great scientist, with so many magnificient achievements to her credit, finding it worthwhile dealing with a problem simple enough to be assigned to a graduate summer trainee! That in

some ways illuminates an aspect of her approach to scientific research. She did great things, but never insisted that she would do only great things. She enjoyed every bit of her work, whether it be on the complex vitamin B_{12} or a simple cyclohexane derivative.

The volume contains some excellent biographical sketches on Kathlene Lonsdale and J. D. Bernal, in addition to an obituary on Dorothy Wrinch. All the three have influenced Dorothy greatly and all of whom she knew intimately. The biographical memoirs on Bernal and Lonsdale, written in Dorothy's inimitable intimate style, are small volumes by themselves. The subjects come alive in them.

The articles on Dorothy by a selected few of her colleagues and friends from different parts of the world are a very valuable feature of these volumes. These articles are written by Jack Dunitz, Max Perutz, David Phillips, B. K. Vainstein, S. Ramaseshan, Dongcai Liang and Chih-chen Wang and Guy Dodson. They discuss, all in very affectionate and intimate terms, the many facets of Dorothy's life, family and personality, her style as a scientist, the ambience of her Oxford laboratory, their relationship with her, her visits, her influence on the development of science in different parts of the world.

While reviewing a book by Sir Lawrence Bragg, Dorothy wrote (Vol. III. p. 618): 'This book is a joy to read. Over and over again one can almost hear W.L. Bragg talking, as he used to talk when he was with us. . . .' The same could be said about Dorothy's writings. This is particularly true about the unfinished autobiographical memoirs at the end of Vol. III. She writes about her family background, her birth in Cairo, her schooling in England, her stay in Sudan and Jerusalem where her father worked, her fascination for chemistry and archaeology and much else on her early life. Then there are her student days at Sommerville (Oxford) and her introduction to crystallography, all discussed in the historical setting. She writes about her short momentous interlude at Cambridge, which probably set the stage for her illustrious future career, and her work and association with Bernal. She returned to Oxford after a couple of years at Cambridge, to set up her own laboratory and career. In her narrative, as indeed in her life, science, friends and family all become parts of a harmonious whole. She describes how she met and got to know Thomas Hodgkin, her husband, their attempts to set up home, though having jobs at different places, and the birth of Luke, their first son. There are references to their homes at Oxford, 315 Woodstock Road and 20C Bradmore Road, and above all to Crab Mill at Ilmington, landmarks so very familiar to her students, colleagues and friends. There are references to the beginnings of her rheumatism which troubled her throughout her life. Then there are accounts of the beginnings of the Second World War and its unsetting effects. Her early exciting work on protein crystallography, the solution of the structure of cholesteryl iodide and many other interesting investigations were carried out during this period when Dorothy and Thomas were settling down at Oxford along with their son, in a rather unsettled environment. The memoirs conclude with the penicillin story, the vicissitudes during the investigation and how the β-lactam structure was finally arrived at by the end of the war. The memoirs cover only the first 35 years of Dorothy's life and less than 15 years of her illustrious scientific career. One wishes that she remained well enough to complete the story!

The editors and the Academy deserve congratulations for producing these splendid volumes which are sure to be of abiding interest to scientists and those interested in science in general. They would be of particular value to crystallographers, chemists, structural biologists and historians of science. To those of us who have had the good fortune to work closely with Dorothy and to know her intimately, the volumes bring not only enlightenment, but also joy and happy memories.

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