Dorothy Crowfoot Hodgkin – An introduction to her work and personality

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I had intended to begin this preface by declaring that Dorothy Hodgkin is one of the most remarkable woman scientists of the century. On thinking it over, however, I started to have doubts about the exact phrasing. I realized that the intended tribute might be interpreted as containing a slightly condescending element – quite the opposite of the impression I wanted to convey. Having been brought up in a past era, I am never sure whether compliments of this kind, with the gender classification included, are 'politically correct' or not, whether the restrictive adjectival 'woman' will be interpreted as augmenting the praise, detracting from it, or as neutral, as a simple matter of fact. I trust that readers will accept it as I intend it; as essentially neutral with a very slight element of augmentation, because, after all, in our times and even more when Dorothy was young, it was more difficult for a talented woman to become a scientist than for an equally talented man. In any case, Dorothy belongs in a small group of women who have changed the face of science, as will be abundantly clear from the papers in this collection. The early work in small-molecule crystallography developed naturally into macromolecular crystallography; for me, the landmarks are cholesterol, penicillin, vitamin B_{12}, and insulin, with excursion into the surrounding areas.

In an earlier essay in the volume commemorating Dorothy's 70th birthday, I tried to explain why I thought she had a special place in 20th century science, chemistry in particular. In the first place, she was perhaps the foremost proponent of the idea that the structure determination of complex molecules was more a matter for X-ray crystallography than for traditional chemistry. This may seem commonplace today, but it was not always so. Dorothy not only propounded this idea, she also showed how it was to be put into practice. This was before the advent of nuclear magnetic resonance methods, which soon found a place in nearly every chemistry laboratory to check structural assignments of molecules and to fit in missing details where these were not known. The combination of spectroscopic and diffraction methods helped to liberate chemistry from the burden of structure determination and allowed its practitioners to apply their imagination and ingenuity to advance into new areas. I take here the liberty of defining molecular biology as one of these areas. Of course, Dorothy's work was not done in isolation and owed much to the example and inspiration set by her contemporaries: Bernal, Bijvoet, Pauling, Perutz, Robertson, and others.

Dorothy grew up at a time when chemists argued and even quarreled about the structures of natural products. At meetings of older natural product chemists, one can still hear nostalgic accounts of how A showed that the structure of some compound deduced in B's laboratory was incorrect; a year later B turned the tables on A by showing that the revised structure was still in need of further correction. Reputations could be bruised, feelings could be hurt, and enmities could be created. In contrast, structures determined by X-ray crystallography rarely led to quarrels. They had a satisfying impression of definiteness about them, in contrast to those inferred from chemical reactivity patterns. Molecules were revealed to correspond to objects of definite size and shape, not just intellectual constructions designed to explain chemical reactivity. The price to be paid was that in the course of determining the structure of a compound by crystallography, no new chemistry was done, nothing new was learned about the chemical reactivity of the compound in question. On the whole, however, the liberation of chemistry from the burden of structure determination has opened the way to undreamt advances in synthetic chemistry. Freedom from the task of structure proof has meant freedom from the restriction that a synthesis of a given target molecule had to proceed by steps of known reaction type. Thus, synthetic strategies no longer need to follow along well-established lines but can be of an outspokenly exploratory nature.

In this development, Dorothy's contributions are distinguished by several characteristics that led to her being acknowledged as the leading crystallographer in the field of natural product research. One was her unerring instinct for sensing the most significant structural problems in this field. These problems were usually the difficult ones, the ones that most scientists with any sense would tend to avoid as being insoluble. This brings us to the second characteristic, her audacity in tackling problems that seemed virtually hopeless; I remember the early days of the work on vitamin B_{12} and on insulin, it seemed to me at the time that it would never lead anywhere – but then I am a pessimist and give up all

too easily. Dorothy did not give up, and the third factor in her personality was her perseverance to keep going when others would have resigned. She was an optimist in the sense that she was convinced that something would turn up, some new advance that would lead to a solution to the apparently insoluble problem. And she was often right. The vitamin B_{12} work, and even more the insulin work, could never have been completed with the technical facilities that were available when these researches were begun. But the needed improvements in computational possibilities and in the techniques of structure analysis happened, and, as they became available, Dorothy was ready for them, she could put them to immediate use. And then, perhaps most characteristic of all, there was the remarkable skill, experience, and imagination she applied in order to put together the pieces of the puzzle once they began to take shape. As David Phillips has written, Dorothy was the arch-exponent of interpreting Fourier maps: 'Anyone who has seen her at work, surrounded by carefully drawn maps and absorbed in their interpretation, has been privileged to witness an artist in action as, with incomparable insight, she *turns them into shapes, and gives to airy nothing, a local habitation and a name*'.

In this context, it may not be out of place to describe some of my own personal recollections of Dorothy and of her laboratory during the mid-1940s. Towards the end of my doctoral work with J. Monteath Robertson at Glasgow, there were rumours that the structure of penicillin had been established by crystal structure analysis in Dorothy's laboratory in Oxford. This had been achieved, so it was said, in the absence of a known chemical formula for the molecule, and even, it was hinted, in opposition to the conclusions drawn from the chemical evidence. This seemed like a miracle. At any rate, it was obvious to me that such an accomplishment could not have been carried out by the methods we used in Glasgow. For our trial-and-error methods we needed a well-defined molecular model. Although Robertson himself had shown the power of isomorphous replacement in crystal structure analysis 'heavy atom' methods were not current among his students. We had heard of the Patterson function, but the only applications we knew were for very simple structures. We could prove that it would not work in more complicated cases. We were conditioned to think in terms of two-dimensional projections rather than in terms of the three-dimensional structure itself. I read some of Dorothy's published papers, especially the one (with Harry Carlisle) on the structure analysis of cholesteryl iodide, involving the use of three-dimensional diffraction data. I saw that three-dimensional methods were essential for the solution of complex organic structures and decided to go to the Oxford laboratory to learn how to apply them in practice.

In the late spring of 1946 I wrote to Dorothy Crowfoot Hodgkin at the Chemical Crystallography Laboratory, University Museum, Oxford, to ask about the possibility of doing post-doctoral research with her, and I also wrote to the Carnegie Trust to ask if the research stipend I received to support my work with Robertson might be extended for a period to allow me to study with Hodgkin. Dorothy wrote me a friendly letter back, and the Carnegie Trust replied that it was prepared to support me in the way I asked. That summer I went to Oxford for a day or two to discuss details of my forthcoming stay.

Some memories of my first meeting with Dorothy are still quite vivid. At the Porter's Lodge of the splendid, neo-gothic University Museum I was directed to her room, just across from the collection of life-size skeletons of prehistoric animals, including Tyrannosaurus Rex with its fearsome jaws. When I knocked on the door, punctually, at the agreed hour of the afternoon, Dorothy greeted me with her serene, pre-Raphaelite smile and explained that she was just concluding a tutorial. As the two Somerville students were preparing to leave, one of them enquired politely, 'And when should we come back for our next tutorial, Dr Hodgkin?'. Dorothy seemed to consider the question with great concentration before replying, 'Tuesdayish.' 'And at what time should we come?'. 'Threeish'. This was my introduction to a way of expression that was quite characteristic of her. Studied vagueness? It may have been studied, but it was not vague.

In October 1946 I moved to Oxford with my modest stipend from the Carnegie Trust. The Chemical Crystallography Laboratory was housed in a set of rooms in the Museum. The experimental facilities, X-ray tubes, X-ray cameras, microscopes, etc. were in a kind of dungeon, enclosed by massive stone walls, close to the northern entrance to the Museum. Hot water pipes ran through the middle of the darkroom, resulting in quite extreme ambient temperature changes, depending on the hot water supply. The room where I had met Dorothy was indeed her office but it also housed her whole research group, including at the time Barbara Rogers-Low, the mainstay of the recently completed penicillin work, later Professor of Biochemistry at the Columbia University Medical School, and Gerhard Schmidt, later Professor of Structural Chemistry at the Weizmann Institute and founder of modern solid state organic chemistry (sadly, he died far too early, in 1971, but the school which he built in that subject at the Weizmann Institute is still thriving). Perhaps we were half-a-dozen in all. To accommodate this group was a large central table, plus several smaller desks round the walls. And above the grand old-fashioned mantelpiece stood an engraved inscription from Hippocrates to remind us of the transience of our life and the hazards of our craft:

ΒΙΟΣ ΒΡΑΧΥΣ. ΤΕΧΝΗ ΜΑΚΡΗ. ΚΑΙΡΟΣ Ο ≡ ΥΣ.

ΠΕΙΡΑ Σ ΦΑΛΕΡΗ. ΚΡΙΣΙΣ ΧΑΛΕΠΗ

At the southern end of the building was the realm of Dorothy's senior colleague, Tiny, otherwise Herbert Marcus Powell, University Reader in Chemical Crystallography (Dorothy's title was then, I think, Demonstrator). This domain comprised a small chemistry laboratory and workshop (where Frank Welch, Tiny's factotum, repaired broken equipment and generally cared for the well running of the laboratory), besides a small lecture theatre that provided office space for Tiny and his co-workers. This was the time when the Powell group was investigating the crystalline inclusion compounds formed by hydroquinone, work that led to Powell's important concept of clathrate compounds.

Another temporary member of the laboratory was Margaret Roberts, a final-year Somerville chemistry student. For her Part II research project, Dorothy assigned her the task of helping Gerhard in his attempts to prepare and crystallize derivatives of gramicidin S, an antibiotic of then unknown structure, now known to be a cyclic decapeptide. Margaret Roberts did not achieve much fame as a structural chemist, but she went on to secure a place in British, European, and world history as Margaret Thatcher.

From time to time, interesting visitors turned up at Dorothy's laboratory. Lawrence Bragg and J. D. Bernal came every few months to hear about our progress. When Bragg came he usually seemed to have forgotten most of what one had told him on his last visit, so one had to explain everything again from scratch. He was not interested in details and was probably thinking of more important matters. Sometimes he came out with a penetrating question about the fundamentals of our craft. Bernal remembered everything he had been told, he asked precise questions and was quick to see connections between one piece of work and another. One day, Max Perutz telephoned to ask whether I would be interested in coming for a day to Cambridge to give a seminar on my Glasgow work. As I recall, the seminars were known as Space Groups in those days. What a fantastic offer! I would actually get my travel and accommodation expenses paid for a visit to a place I had always wanted to visit anyway! No doubt Dorothy had hinted to Max, or to Bragg, that I would greatly appreciate such an invitation.

I should also be grateful to Dorothy for suggesting to Bragg in 1955 that I would welcome an offer to join the research group he was building up at the Royal Institution in London: and again, a year or so later for suggesting to Leopold Ruzicka that I might be a suitable person to build up a new research group in chemical crystallography at the Swiss Federal Institute of Technology in Zurich. Ruzicka had been one of the first to see that X-ray crystallography and other physico-chemical techniques could solve molecular structural problems that would defy traditional chemical methods. He had been impressed by the penicillin work and again, a few years later, by the vitamin B_{12} structure, which, he saw, could never have been elucidated by him or by any of his rivals. He was a great admirer of Dorothy and was prepared to take her advice. So it came about that I went to Zurich in 1957 and have stayed there ever since. Of course, no one dreamt then that vitamin B_{12} would lead to another link between Dorothy and the ETH organic chemistry laboratory.

In my opinion, the B_{12} structure is Dorothy's greatest achievement. Although Dorothy herself would probably give first place to the insulin structure, which had preoccupied her almost from the beginning of her career, my preference is different. By the time the insulin structure was actually solved in 1969, the structures of several other proteins had been elucidated. Although we were all aware of the significance of the insulin work, we had become accustomed to seeing the structures of other, still more complex protein structures, and we were anyway more or less expecting the insulin structure to emerge. It did not bowl us over. The B_{12} structure was different. It was of a level of complexity that had never been seen before among natural product structures, and it was the opening into a new world of possibilities, as aptly expressed in 1977 by my colleague Albert Eschenmoser:

'When Hodgkin announced the complete structural formula of vitamin B_{12} in 1956, it was clear that this natural product presented an ideal objective for organic synthetic research. It is a compound of great biochemical significance. Its molecular architecture is complex and had not previously been encountered in natural products chemistry. Its structural nucleus had resisted elucidation by means of chemical methods of degradation and had been solved by X-ray crystallographic analysis. The synthetic investigation of vitamin B_{12} would involve a host of new problems in the realm of planning and method and would link 'X-ray island B_{12}' with the mainland of chemical experience. Vitamin B_{12} provided an opportunity to extend the frontiers hitherto established by organic synthesis in the area of low-molecular-weight natural products.'

I am probably not alone in looking back at the period before direct methods, before modern computers and diffractometers, at a heroic time with Dorothy as one of the heroines. The goals then, penicillin, vitamin B_{12}, insulin, hemoglobin, myoglobin, seemed almost impossible to attain, and when they were reached they revealed the secrets of nature at higher and higher levels of complexity. Of course, in structure research, as elsewhere, every age is a heroic time, W. H. Bragg attempting the crystal structures of naphthalene and anthracene in 1921

'in order to discover, if possible, some way of handling the complex molecules'; Perutz attempting to derive information about the structure of hemoglobin from three Patterson projections; Watson and Crick attempting to guess the structure of DNA by speculative model-building using stereochemical arguments – and even succeeding. In more recent times we have seen the structure of the photosynthetic reaction centre of a bacterium, providing a structural basis for electron transfer in biological systems – who would have thought it possible! And, looking, into the future, in a few years we may have the structure of the ribosome, the protein manufacturing factory. Yes, we live in marvelously exciting times. And the volumes containing Dorothy Hodgkin's collected papers may serve as a monument to those times. One hopes that they will not only be of interest to historians of science, but also even more that future generations of budding scientists will find in them inspiration and courage to come to terms with whatever problems they may have to face.

Forty years' friendship with Dorothy

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Example is not the main thing in influencing others, it is the only thing.

—A. Schweitzer

THE four people who took an interest in my early X-ray work on haemoglobin were J. D. Bernal, W. L. Bragg, D. Keilin, and Dorothy. Bernal would listen intently, make some profound comments, and then suddenly sweep off with the air of having to do something far more important. Bragg would discuss the interpretation of my X-ray patterns, but he knew no protein chemistry and not taken any X-ray pictures himself for many years. Keilin was a biologist, and X-ray crystallography was a closed book to him. So whenever I obtained exciting new results, or was disheartened by the persistent lack of them, I would take the now extinct branch line from Cambridge via Bedford to Bletchley and hang around at that dismal junction until the ancient rattly train set off on its many stops to Oxford.

Once arrived, I made for Ruskin's Cathedral of Science – the University Museum – walked past the skeletons of extinct species populating its nave to the darkest corner, and descended the stone stairs to Dorothy's crypt-like office, where she laboured on the structure of life in a place that was, but for her vitality, quite dead (Figure 1). Her tables were piled high with structure-factor and Fourier calculations; there were viewing boxes for looking at X-ray pictures. Her X-ray and dark rooms were adjoining. The gothic window was high above as in a monk's cell, and beneath it there was a gallery, reachable only by a ladder, on which stood a table with Dorothy's polarizing microscope. To mount one of her precious crystals of penicillin, Dorothy would climb up there, stick the crystal to a thin glass fibre, stick the fibre to a goniometer head, and descend again, clutching her treasure with one hand while holding on to the ladder with the other. I don't think she ever lost a crystal.

For all its gloomy setting, Dorothy's lab was a jolly place. As Chemistry Tutor at Somerville she always had girls doing crystal structures for their fourth year and two or three research students of either sex working for their Ph Ds. They were a cheerful lot, not just because they were young, but because Dorothy's gentle and affectionate guidance led most of them on to interesting results. One exception was a certain Margaret

Figure 1. Dorothy when I first knew her.