'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

Max Perutz

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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.

Roberts whom Dorothy asked to have a shot at gramicidin S, a cyclic decapeptide which Dorothy may have, hoped to solve more easily than proteins. Perhaps Margaret Roberts' failure contributed to her decision to turn to law. When she came to visit our laboratory as Prime Minister some 35 years later, I showed her the structure and told her that it had not been solved until the late seventies when Michael Woolfson's direct methods finally cracked it. However, this consoling piece of news did not make her revert to a career in X-ray crystallography. Despite their political dissension, Dorothy and Margaret Thatcher have maintained a warm regard for each other through all these years. We looked at their latest organic structures and argued about the meaning of our Pattersons of insulin and haemoglobin until it was time to go home to her house in Bradmore Road.

Some women intellectuals regard their children as distracting impediments to their careers, but Dorothy radiated motherly warmth even while engaged in writing crystallographic papers. Concentration comes to her so easily that she can give all her attention to a child's chatter at one moment and switch to lattice transformations the next without any sign of strain. Once she helped her three-year-old son search for a lost toy when he said: 'It must be somewhere; it can't be nowhere.' Not surprisingly he became a topologist. Later in the evening Dorothy's husband, Thomas, would appear if he was not away lecturing to Workers' Educational Association and he would keep us all in fits of laughter over dinner. Afterwards I would discuss proteins with Dorothy until it finally dawned on me that I was exhausting her and that it was time for bed. On Sundays we would go walking or swimming in the Isis. Many years later the two families, six Hodgkins and five Perutzes, went on holiday together to the Austrian Lakes. Once when we had to take shelter in a storm Thomas kept on inventing such good games and stories that he made us feel sorry when the downpour stopped.

Sometimes Dorothy invited me to Oxford to see her latest results. There was cholesterol iodide. She and Harry Carlisle found the iodine positions from a Patterson and used them to calculate the signs of the (*h*0*l*)s of the monoclinic crystals. The resulting projection showed the molecule well resolved. To determine its stereochemistry, Harry then recalculated the Fourier along a set of lines drawn through each peak perpendicular to the plane of projection. This Fourier was again done with phase angles based on the iodine positions alone, which imposed a false centre of symmetry on the map. With careful stereochemical reasoning and insight, Dorothy picked out the correct one among the two alternative atomic positions indicated for many of the atoms and brought to light the first complete stereochemically correct formula of a sterol. Then came penicillin. Dorothy writes that its revolutionary β-lactam structure had actually been the first proposed, but Robert Robinson was strongly against it because β-lactam rings are generally stable, unlike penicillin, and J. W. Cornforth, then a post-doctoral fellow, supported Robinson's view at an early stage, saying: 'If penicillin turns out to have the β-lactam structure I shall give up chemistry and grow mushrooms'. Luckily he did not carry out his threat and won the Nobel Prize for Chemistry eleven years after Dorothy. The difficult step in the initial structure analysis was to pick out the right lumps of density representing one molecule. Dorothy had a shot at it and then asked others, including myself, to find it. Her first guess proved correct, and further refinement brought to light the β-lactam ring. She writes: 'It was a nice day when we could set up the model first precisely in three dimensions and ring up our friends to come and see what penicillin actually was.'

It was the same with vitamin B_{12}. Anyone else looking at her first Fouriers, derived from the cobalt phases alone, and later from the cobalt plus selenium phases of a selenocyanide derivative, would have attributed the close approach of two lumps of electron density to experimental error, but Dorothy combined a firm belief in the significance of even very blurred features of electron-density maps with a profound flair for the chemically reasonable, and she concluded rightly that the lumps represented rings linked directly rather than through a methene bridge as in porphyrins. She recalculated her phases from the positions of the cobalt plus the atoms of what she later christened the corrin ring, with the result that the next Fourier revealed much of the vitamin B_{12} molecule in outline.

But was it right? On 28 December 1954 Dorothy wrote to me (Figure 2):

We've had one very nice development on the B_{12} front. Lester Smith fed dichlor-benzimidazole to his bugs and got them to synthesize a chlorine substituted vitamin B_{12}. We had encouraged him to make the dibromo compound but he had difficulties with making the dibromobenzimidazole – and anyway we find that we can see what we want without it. On the very first photograph we took of the dichloro compound there were recognisable small intensity changes on which I straight away did a nice little calculation. It runs like this.

032	042	
+11	−16	F/4 obs. for dry B_{12}; signs on proposed str.
c+10	c+1	Changes in F expected on substitution of Cl for Me
c+21	c−15	F/4 values ∴ expected for dichloro cpd.

Observed on first photograph 032 stronger than 042 (both quite weak). The Cl contribution to 032 is almost the maximum.

Most of the reflections have not visibly changed to the eye. But we shall now have to work up the photographs properly – the expected differences are, of course, usually very small. Cl-Me! But it does seem that this very first observation and calculation confirms that we have quite correctly placed the nucleotide – and this carries with it at least one piece of chemical information, the 3-phosphate binding. Also of course it makes me more than ever confident about everything else.

I have been turning my mind to insulin, thinking B_{12} is drawing to an end and I would like to take up insulin seriously and properly. I

am not very happy about one's power of model building – even with all the information we have. I gather Lindley and Rollett at Cal. Tech. have built an α helix model, I imagine with parts of chains in helices – I have asked for details But I would like to work it out properly and I think it can be done with distributed heavy atom derivatives – and a number of years' We have one or two ideas on the heavy atom front which we hope to try out in the next few months. I find myself wondering if the biosynthetic approach is a possible one – easier perhaps to think of for haemoglobin than for insulin.

Ever since she took her first X-ray pictures of insulin in 1935, Dorothy continued to think about its structure. On 26 April 1949 she wrote to me:

I am very much interested that you have taken up the threefold spiral structure. It certainly is a nice one. Kate [Dornberger-Schiff] and I spent a long time once doing sums on insulin intensities, trying to fit a particular form of it into our picture. Actually when I looked back on those four calculations they seemed not unhopeful – and yet I don't somehow feel in my bones that they are right. And I did some time ago a theoretical Patterson of it – which has quite a lot of good features but doesn't, I think, fit for the gramicidin S.

When Sanger had determined the positions of the disulphide bridges in insulin, I sent her a preprint of his paper. She replied on 20 July 1955:

Thank you ever so much for sending me the insulin paper. It is terribly important – Sanger finds the internal link to be 6 : 11 and this, it seems to me is fatal to simple helical models. Even 7 : 11 I never much liked. Indeed the more one thinks about the geometry of cystine the more one is driven to β type chains (Astbury has said this). I've built a total model for insulin nicely and smoothly and quickly on one of the very oldest schemes anyone has ever had, short folded lengths of β chain (anti-parallel pleated sheet type), in the same configuration that I favour for gramicidin S.

It was another fourteen years before I had a telephone call (Figure 3) from Guy Dodson inviting me to Oxford to celebrate the solution of the insulin structure. I rushed there with a magnum bottle of champagne which someone had given me as a belated present for my Nobel Prize, but when we extracted the cork, all the CO_2 had evaporated and it tasted, as David Phillips remarked in his usual tactful way, just a little peculiar. Then Dorothy showed me that the Patterson of insulin, on which she had spent so much thought, contained near its origin a simple symmetry-duplicated image of the histidines surrounding the central zinc atom which she could easily have interpreted if only she had applied to it her usual faith and courage.

Sometimes I asked Dorothy to visit me in Cambridge. In the summer of 1953 I had just determined the signs of the ($h0l$) reflections of horse methaemoglobin by isomorphous substitution with paramercuribenzoate and had calculated the first Fourier projection of the molecule. Dorothy came over at once to admire my map, even though she realized that the many overlapping features of the 55 Å thick molecule would render it uninterpretable. Then she said to me: 'If you could get two heavy atom derivatives, you could solve the structure in three dimensions' and drew my attention to Bijvoet's paper on strychnine in which he pointed to the possibility of solving the phase equation by double isomorphous substitution. This remark sent me off on the next stage of the haemoglobin work. Luckily I did not foresee that it would be another six years before Dorothy would ring me up saying: 'I hear you have a fantastic model of haemoglobin. Can I come over and see it?'.

I felt embarrassed when I was awarded the Nobel Prize before Dorothy, whose great discoveries had been made with such fantastic skill and chemical insight and had preceded my own. The following summer I said

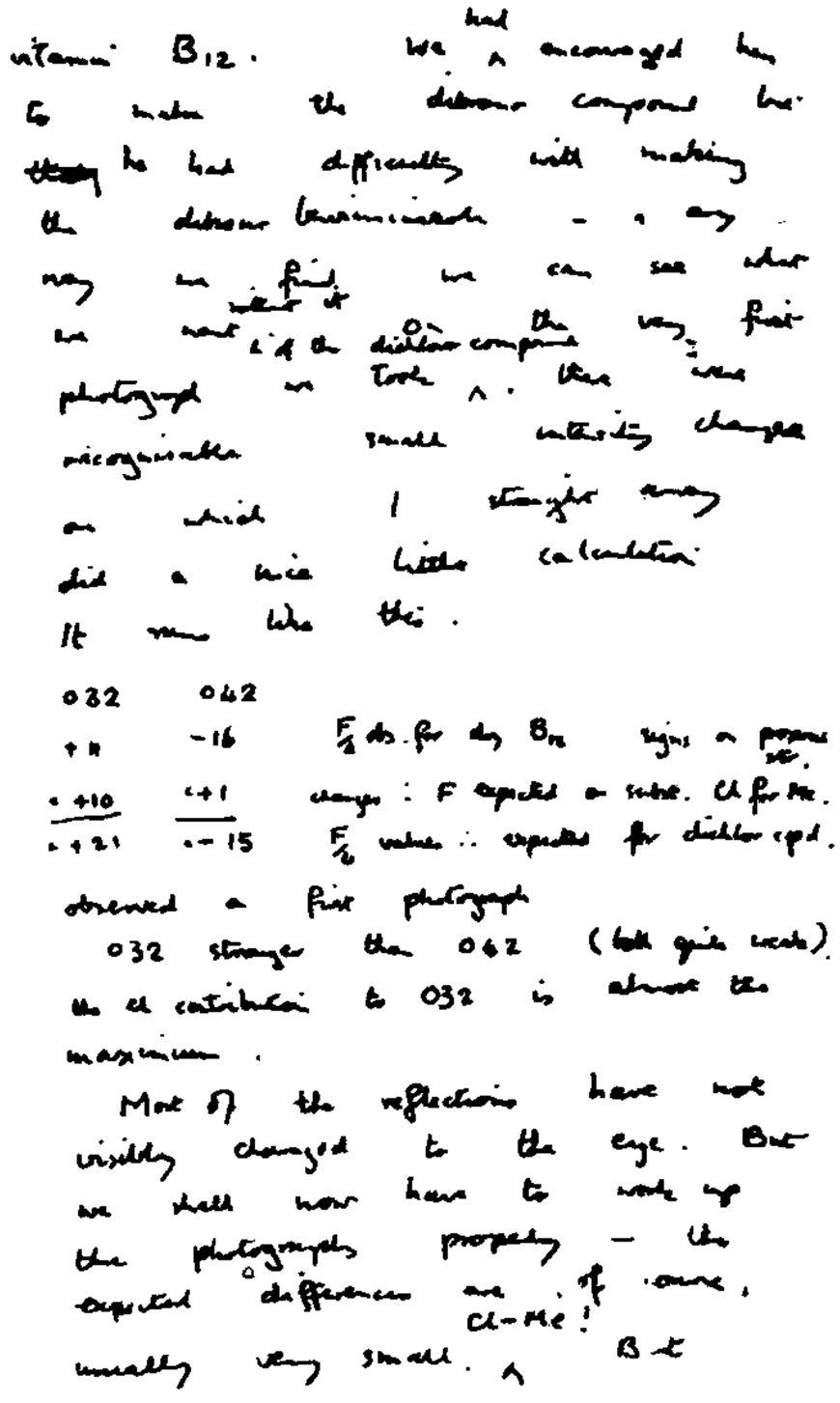
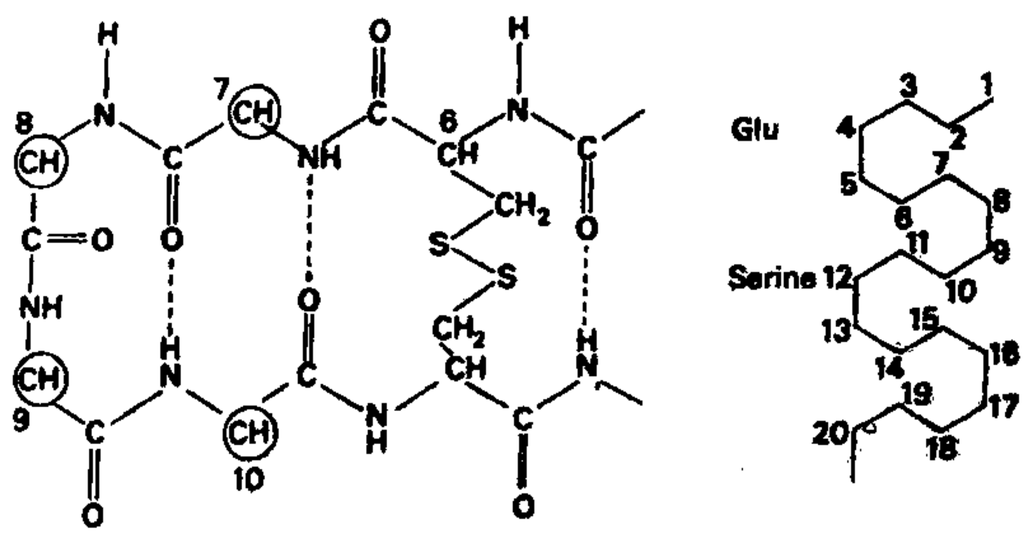


Figure 2. A letter written by Dorothy.



Scheme.

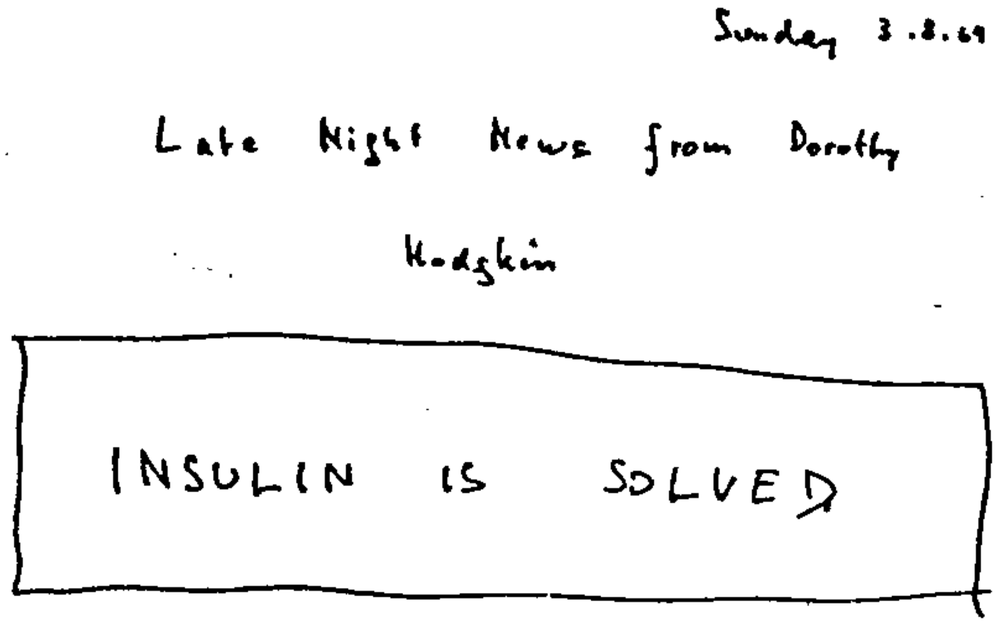


Figure 3. Poster at the Laboratory of Molecular Biology, Cambridge, announcing the great news.

as much to the Swedish crystallographer Gunner Hägg when I ran into him in a tram in Rome. He encouraged me to propose her, even though she had been proposed before. In fact, once there had been a newsleak that she was about to receive the Nobel Prize, but it proved false; Dorothy never mentioned that disappointment to me until long after. Anyway, it was easy to make out a good case for her; Bragg and Kendrew signed it with me, and to my immense pleasure it produced the desired result soon after.

'There are certain letters which I dread to open', Dorothy once told me, 'and when I saw one from Buckingham Palace I left it sealed, fearing that they wanted to make me *Dame* Dorothy'. I suppose it would have made her feel like a *femme formidable*, which she so happily is not. When she eventually opened the letter she was relieved that instead the Queen offered her the Order of Merit, which is a much greater honour and carries no title. She received it in private audience on the same day as Benjamin Britten. Once when they were both getting honorary degrees, Henry Moore said to her: 'It's really very good of them to give the OM to a simple chap like me.' I suspect that this remark echoed some of Dorothy's own feelings.

Dorothy Hodgkin and molecular biophysics in Oxford: A fragment of personal history

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THE Laboratory of Molecular Biophysics had its origins at the Royal Institution, London, in the group that Lawrence Bragg assembled there when he became Resident Professor and Director of the Davy–Faraday Research Laboratory in 1954. During the preceding years in Cambridge, Lawrence's main interest had been in the studies of protein crystals by Max Perutz, John Kendrew, and their colleagues, and he had involved himself deeply in the work of the group during the period when very few crystallographers believed that it was likely to be successful[1]. When he left Cambridge in January 1954, however, the tide had turned dramatically. A few months earlier Max, with David Green and Vernon Ingram[2], had shown how the method of isomorphous replacement could be used in protein crystallography and the way seemed open to the detailed determination of protein structures—starting with Max's haemoglobin and John Kendrew's myoglobin. Even the computational problems no longer seemed insurmountable with the growing power and availability of digital computers[3].

Bragg would have liked to take Max and John with him to London to continue the work there, but, at this critical time with so much to be done to exploit the breakthrough, neither was willing to leave Cambridge. But they promised to help Bragg assemble a new group at the Royal Institution and to co-operate closely in its work. At this stage Uli Arndt was already at the Royal Institution, where he had been studying proteins by low-angle scattering with Dennis Riley[4] and developing experimental methods. Early in 1955 he was joined by Helen Scouloudi, who had worked on ribonuclease crystals with Harry Carlisle and now began her study of seal myoglobin. In the autumn, David Green joined the Group from Cambridge and Tony North came from King's College London, where he had worked with J. T. Randall and Pauline (Cowan) Harrison on collagen.

These recruits all had experience of protein work, of one kind or another, but the original team was completed at the end of 1955 by the addition of two more who had not worked directly on proteins. This was Dorothy's doing. Anxious to build up a really strong group at the Royal Institution, Bragg had also asked Dorothy if she would join him there, but she was not prepared to leave Oxford at a time when her family commitments were