

was really a home to all of us. Someone from some corner of the earth was always also there. We could stay there as long as we liked – breakfast, lunch, dinner (Thomas always made vegetarian dishes for us). All sat together and relaxed in the garden; Dorothy showing us some manuscript of hers for an opinion. Thomas having heated arguments on the state of world. Or we would go to dine with Dorothy's remarkable mother-in-law who lived in a beautiful house up the road when she would tell of the naughty things that happened in the early part of the century at the university. Dorothy's

greatness does not rest on her having solved cholesterol, penicillin, B<sub>12</sub> or insulin. True, these are unparalleled achievements. But to many of us her greatness also lay elsewhere which made her spread her science to all parts of the world and also in her concern for humanity. All pay lip services to the cliché, 'We must love humanity'. But Dorothy's method of doing this was like that of Gandhi or Mother Teresa, to have compassion and a personal affection for every fragment of humanity – young and old, wherever and whichever corner of this world it was found in.

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## Dorothy and insulin crystallographic research in China

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ALTHOUGH only two of us have the privilege to be the authors of this article, we believe that many other Chinese scientists, who know Hodgkin either personally or by her fame as a great scientist, have the same wish to express their respect and esteem. Dorothy Hodgkin is to us a dear friend who has given us help and support in our work. What we express here is only a small part of what Dorothy's many friends in this country wish to say.

One of us, Dong-cai Liang, crystallographer, worked on seeking heavy atom derivatives of insulin crystals in the Department of Zoology, University of Oxford under the guidance of Hodgkin in 1966. 'It was an unforgettable experience in my life, at Oxford with Dorothy' Liang told his colleagues and students. 'There I was, the first scientist from Red China in Dorothy's international laboratory, a man from Canton with black hair and a small pair of hands, thanks to which I was able to mount crystals into the capillaries quickly and accurately, and this impressed Dorothy.'

Last May, Liang was told by Guy Dodson that Dorothy wished to come to China this summer for the 16th International Crystallography Congress. We were delighted at this news and Liang made a great deal of effort to bring her to the meeting in China. Nevertheless, considering her age, we were a little concerned about her health during the long journey from Oxford to Beijing. Furthermore, the big gathering of crystallographers from all over the world would no doubt give her a very busy and exhausting time. How could we fail to understand her? She would go not only to Beijing

but even to the ends of the earth. Her age, the hot weather, the long journey, all these are nothing compared to her science. Science is her life! We could not wait to see her again, in China, for the eighth time.

In the 1950s, many Western people knew very little of China, and even less about Chinese science. Dorothy first came to China early in 1959 with her husband, Thomas Lionel Hodgkin, cherishing her intrinsic sense of duty for human progress and civilization and her enthusiasm for people and science in developing countries. In 1965 she visited China again.

In 1967 a group of young Chinese crystallographers started an X-ray crystal structure analysis of insulin in Beijing, stimulated directly by the successful achievement in the total chemical synthesis of bovine insulin with full biological activity in 1965. This was accomplished by a joint group of Chinese biochemists and organic chemists, and also enlightened by the insulin crystallographic research in Dorothy's laboratory. In 1971 and 1973 we obtained the isomorphous replacement electron density maps of insulin in rhombohedral 2 zinc insulin crystals at 2.5 Å and 1.8 Å respectively. In 1972 Dorothy visited China for the third time, this time bringing with her the Oxford electron density map of insulin, as she knew that the Chinese scientists were determining the three-dimensional structure of insulin. Indeed, we compared in detail our electron density maps, as both maps were drawn at a scale of 1 cm to 1 Å, so there would not be many difficulties in cross-checking them. But, there was actually a moment of acute concern when we first put the maps together and found they were not

the same at all! What was the matter? Then it suddenly came to light that one map was upside down compared with the other! This released the tension and everyone breathed again. Later we were happy to find that there was a very good, if not exact, correspondence between the two maps. From then on we always mention 'molecule I Oxford, molecule II in Beijing' when we discussed the insulin dimer structure, because comparison with the Oxford model is unavoidable. During her stay in China, Dorothy went to Shanghai to discuss insulin structure and function relationships with scientists in the Institute of Biochemistry. She continued her travels by flying east to Japan to the 9th International Crystallography Congress. In her lecture there, she kindly spoke of her visit to Beijing and Shanghai, and the results of insulin research in China. This opened to the world the first window of the long isolated Chinese crystallography research. We shall never forget that it was Dorothy, with her noble character and high prestige, who brought the research of the Chinese crystallographers to the international scientific community.

In 1974 the Beijing group reported the detailed crystal structure of insulin at 1.8 Å resolution, and the Shanghai group reported on the interactions of insulin with its receptor in liver and fat cells. These were published in the same issue of *Scientia Sinica*, the leading Chinese journal for natural sciences. Shortly after that we were surprised to read a paper in *Nature* (1975, 255, 103) by Dorothy Crowfoot Hodgkin entitled 'Chinese work on insulin', which commented on the two papers mentioned above. We could only publish our results in domestic journals at that time, and very little was known of these overseas, even of the leading journal *Scientia Sinica*. At that time, under the shadow of the Cultural Revolution, we had to quote from Marx, Engels and Chairman Mao, even in the scientific papers as 'guiding references'. Earlier work on the total chemical synthesis of insulin was also only to be published in *Scientia Sinica*, which made it difficult for the Western world to know what was happening in science in China. Dorothy introduced the achievements of Chinese scientists to the world at an auspicious time through *Nature*. We realize that Dorothy's belief is truth, Dorothy's life is science, she is always enthusiastic about new findings of truth and appreciates scientific achievement whatever its origin.

In this paper in *Nature* Dorothy evaluated our insulin work as follows: 'The present Peking map at 1.8 Å resolution is the most accurate map available of the insulin electron density defined by experimental, isomorphous phase angles... and may well remain so'. We knew the Oxford group was actually carrying out the calculation at 1.5 Å resolution at that time. Dorothy's modesty always impressed us; when she took her first X-ray picture in 1935 many of us were not even born.

She never looks down on any small and young group from the superior position of the Oxford group; on the contrary she always shows her concern, gives scientists like us in developing countries encouragement and discusses matters of common interest with us on an equal footing. She said 'One might not wish, in all cases, to see complete duplication of the X-ray analysis of a protein molecule—so much work is involved. But there are great gains in the present case from having two views of the insulin crystal structure.' She has paid close attention to science in China and made very positive comments on a sequence of scientific publications Chinese scientists achieved since 1961, including the total chemical synthesis of bovine insulin, and on collaborations in different disciplines and laboratories. At the end she suggested: 'It will be splendid if we can some day soon all meet and talk over the very interesting observations that are accumulating, East and West, on the structure and function of insulin.'

Dorothy visited China for the fourth time in 1977 accompanied by Guy Dodson. We occupied most of her time here by asking a lot of questions and discussing insulin structure with her. Her very helpful advice was of great value to us.

Chih-chen, the other one of us, a biochemist, was a young member of the insulin group in 1977, but was very lucky to be asked by Liang to take care of Dorothy and Guy during their stay in Beijing. This gave Chih-chen a special chance to be with Dorothy more than any other Chinese scientist can have. In China, a lady is not first, as in the West, but 'elder is first'. Dorothy is an elder and also a lady, and according to traditions in both the West and the East, she should be double FIRST. Even more, she is a great lady and a Nobel Prize winner. All these made Dorothy so great in Chih-chen's eyes, that it is not an overstatement to describe Chih-chen, when she met Dorothy for the first time, as filled with reverence and awe. Moreover, in 1977, only a few people who had studied English before 1949 could speak good English. Obviously it was not easy for Chih-chen to communicate fluently with Dorothy. In Chinese Chih-chen usually has a ready tongue, but then, in front of Dorothy's 'Oxford English' (which everyone knows in China as the standard and most elegant English) she became tongue-tied. Within a very short time however, her awkwardness was swept away by Dorothy's kindness, elegance and affection, and above all by her tolerance.

One day Dorothy visited her old friend Rewi Alley in a quiet typical Chinese bungalow located close to the commercial centre of Beijing. Alley had worked in China for dozens of years and contributed most of his life to Chinese affairs. Dorothy examined a small piece of antique China with great interest, and could not decline to accept it as generous gift from Alley.

On the other side Chih-chen got a present from Dorothy. It was a small piece of dark coloured pottery from Dorothy's home town, as Dorothy told her. It was a treasure to Chih-chen and she put it in the middle, the most noticeable place of the cabinet for keeping all her treasures. She explained to all her friends where this plain-looking art piece was from, with respect and pride. Every gentleman in our group got a T-shirt with an insulin molecule printed on the back, but nobody has ever seen them wearing it. For us Chinese, treasures are for keeping in a safe place and certainly not for wearing.

Two years later Chih-chen worked in Brandenburg's laboratory in Aachen, on a Humboldt Fellowship. She wrote to Dorothy expressing a wish to visit her, and soon after received an invitation from Dorothy. It came in a small envelope with delicate and beautiful handwriting.

In 1979 the Second International Insulin Symposium was hosted by Brandenburg at the Deutsches Wollforschungsinstitut in Aachen. Three Chinese were present among 180 participants from many countries. The Symposium was a great success and Dorothy's wish expressed in her 1975 *Nature* paper materialized. The Proceedings were dedicated to Hodgkin as the wish of everyone working in the insulin field.

Later, in 1980, Dorothy paid her fifth visit to China, accompanied by the Blundells. At the same time, at Dorothy's suggestion, the Sakabes from Nagoya were also invited to Beijing in order to discuss the insulin structure with the three groups together. It was, indeed, a most helpful discussion. However, what we would like to tell is something else. This was Dorothy's fifth visit to China, but she had never found the time to go to the Great Wall, and we strongly recommended that she should visit that Symbol of China. Climbing the Great Wall is quite strenuous work; some parts are very steep, close to 45 degrees inclination. Dorothy was very excited about the climb and very much enjoyed the splendid view of the Great Wall on the towers of beacon fire. Dorothy was happy to become a Chinese 'haohan' which means 'true man', as we have a Chinese proverb 'One is not a true man if one has never been on the Great Wall'. Sakabe seemed to be a very professional cameraman, as good as with his X-ray camera. Many pictures in Liang's album record that happy time. In 1980 Liang had just returned to Beijing from his re-education by way of the Cultural Revolution in Canton, and could afford to invite Dorothy, the Blundells and the Sakabes to his small apartment to have a cup of Chinese tea. It was a great time for Liang's family,

especially for the two children who were very proud to have a picture taken with such great scientists; they looked like two bodyguards standing on either side of Dorothy.

In 1985, when Dorothy visited China for the sixth time accompanied by Guy Dodson, we compared the electron density maps of our two groups once again in Beijing at a high resolution of 1.2 Å in our map and 1.5 Å in that of the Oxford group. The agreement of the two maps was surprisingly perfect. David Phillips commented on the method for expanding and refining the resolution of a protein structure determination in a letter to us later, when he learnt from Dorothy of the perfect agreement of the two maps. These maps were done at high resolution through independent refinement and correction of one protein structure in two laboratories, and indicated that the method can be used reliably, and this provides an impetus to protein crystallography development.

Thanks to Dorothy's help the relationship between Chinese crystallographers and insulin researchers and the international community developed rapidly. We now have close connections with many laboratories through a variety of scientific exchanges. One could often see Chinese in Oxford, London, York, Aachen, Hoechst, Boston, HIL, Eli Lilly, Duarte, Brussels, Tsukuba, etc, and there are also Western insulin people in China.

In the past 25 years starting with the insulin structure at 2.5 Å resolution, we now have a fine structure at 1.2 Å as well as structures of dozens of insulin analogues at different resolutions. We also have structures of other proteins, such as trichoxanthin, D-glyceraldehyde-3-phosphate dehydrogenase, phospholipases and many others. We are currently fairly well equipped to do research on X-ray crystallography structure analysis. A number of graduate students have been trained in our Institute during the past years, and there are now quite a few groups in China engaged in X-ray analysis of biomacromolecules. Dorothy's help and friendship have a rich harvest.

A short time later we were very happy to see Dorothy again in Beijing at the 16th International Crystallography Congress. Now, Ramaseshan kindly sent us a copy of the printed pages before publication. Dorothy has left us for more than one year. The last opportunity we had to arrange her eighth visit to China for the 16th International Crystallography Congress compensated a little our great grief for the loss of her. However, the memory of Dorothy lives forever among the Chinese scientists.