

The Oxford Science Lecture Series

Professor Elspeth Garman

University of Oxford

“Crystallography one century A.D. (After Dorothy)”

12th Dorothy Hodgkin Memorial Lecture

University Museum, Oxford, 9th March 2010

Professor Garman is the President of the British Crystallographic Association. She did her degree in Experimental Physics at Durham, and came to Oxford as a graduate student to do a D.Phil in Experimental Nuclear Structure Physics. She worked in the Nuclear Physics Department as a Research Fellow and Research Officer for 7 years. In 1987 she moved to the Laboratory of Molecular Biophysics to work with Professor Dame Louise Johnson and has been there ever since, working on finding improved techniques for protein crystallography that enable researchers to gain more information from their structures.

Professor Garman’s lecture was a tour de force to a packed house, with latecomers turned away at the door. She described Dorothy Hodgkin as an amazing woman who has featured in a list of the 100 British women who have changed the world over the past 100 years. She was awarded the Nobel Prize for Chemistry in 1964 for her determination by X-ray techniques of the structures of important biochemical substances. She was also a recipient of the Order of Merit and a Fellow of the Royal Society, she was awarded the Lenin Peace Prize and was President of Pugwash. There are buildings named after her at the Universities of Keele, York and Bristol (of which she was Chancellor). In her research she solved the structures of cholesterol iodide, penicillin, vitamin B12 and insulin and her work paved the way for 3D structural measurement in medicine.

Professor Garman described proteins as a string of amino acids, similar to a string of beads and explained that these strings are scrunched up as a complex 3D structure. She then described a crystal as an array of soldiers, each representing a folded protein molecule, standing identically in serried rows. She said that x-ray crystallography worked in a similar way to firing canon balls into the rows of soldiers and observing where they emerged, having either passed between soldiers or ricocheted off one. On occasion the force of the canon balls is so strong that the balls damage the soldiers, and this represents the problem of x-ray damage to the crystal during the process of acquiring the data. X-ray diffraction, or the pattern of emerging canon balls, provides a map of the electron density within the crystal. The order of the amino acids along the “string of beads” is known, and so by combining this information with the electron density map it is possible to build up the 3D structure of the protein. Dorothy had to develop these images on photographic plates and then build up the structure by hand, in a process that took many weeks, finally producing a model constructed with

wire and balls. With the advent of computers, this process can now be done much more quickly and computers provide the opportunity to display elegant 3D structures and to manipulate the molecules to learn more about the function of the protein.

One of the major obstacles to ascertaining the crystal structure of a protein is that of handling the crystals in the x-ray beam. In 1934, Dorothy Hodgkin published a paper in *Nature* with J.D Bernal, reporting that by keeping the crystal damp it was possible to preserve the crystal in the x-ray beam and obtain an electron density map. With the increased strength of x-ray beams over time, however, the problem of damage to the crystals from the x-ray beam has re-emerged and Professor Garman has, in her turn, overcome this problem by suspending the crystals in a fibre loop prior to rapid freezing. She reported that her daughter's hair was particularly useful for this task! The crystals are first grown in hanging drops, suspended over a bath of liquid in a sealed chamber. Professor Garman described how the effect of gravity on the proteins in the solution can affect the efficiency of the crystal growing process and so they predicted that crystals growing in space would form more efficiently. In 1988, they arranged to send a protein from the HIV virus into space to test this theory, which led to an outraged article in *The Star* predicating disaster with the HIV virus disbursed in the atmosphere to infect the entire world!

With the development of increasingly powerful x-ray beams and computers, the number of solved protein structures is growing exponentially. Professor Garman explained how by determining the structure of a protein we can gain information about its function and thereby design drugs to enhance or to interfere with that function. She described her work on the structure of proteins on the surface of the flu virus and how that has led to the development of the anti-viral treatment Relenza.

In conclusion, Professor Garman quoted advice given by Dorothy Hodgkin to new graduates at the University of Bristol: "I hope that some of you will live modestly and do serious things". The audience then moved downstairs to join the dinosaurs for the customary wine reception, in a modest and serious manner, of course.

Dr Carolyn Carr, Cardiac Metabolism Research Group, University of Oxford.