Dr Margery Ord

The defining point in Margery's scientific career was when she arrived in Oxford towards the end of 1951 to take up a post-doctoral position with Lloyd Stocken in the Biochemistry department. This position appears to have been arranged between Lloyd and Robert Thompson, her Ph.D. supervisor at Guy's Hospital, with little or no input from Margery and few would have suspected that it would be the beginning of a lifelong, and in many ways unique collaboration in which they shared many years of scientific research and enjoyed a deep personal friendship.

When Margery joined Lloyd, he was already well known for his role in the identification of an antidote to the chemical weapon Lewisite which, it was feared, might be used during the World War II. However, he had recently changed the direction of his research to study the biological consequences of irradiation, a topic of acute importance following the dropping of atomic bombs on Hiroshima and Nagasaki and the onset of the cold war. His decision to move into this area may have been strengthened by the establishment of the MRC Radiobiology Research Laboratory at Harwell in 1947 where there was a radioactive source suitable for use in their experiments.

At the time, very little was known about the biological effects of radiation. It was known that it primarily affected dividing cells, such as those in the bone marrow and the lining of the gut, and that in these cells, DNA synthesis was impaired. However, it was not clear if the effect on DNA synthesis was the primary event, or just a consequence of impaired energy metabolism and cell death. Margery's first studies, using expertise gained during her Ph.D. project, showed that energy metabolism was not directly altered by irradiation and this led to their subsequent focus on DNA synthesis.

Initially, Margery and Lloyd studied DNA synthesis in irradiated rat thymus cells, which were simple to isolate and from which nuclei could easily be prepared. However, during the course of these studies that it became apparent that the effect of irradiation was significantly different at different stages of the cell cycle. To study this, it was necessary to have cells which were synchronised so that they all were at the same stage of the cycle at the same time. In subsequent research, they used two experimental models in which this synchronisation could be obtained. The first of these was regenerating rat liver. The liver has remarkable powers of regeneration and will quickly grow back after a large part has been surgically removed. During the early stages of regeneration, the remaining liver cells divide rapidly to replace the lost tissue and, as they all start at the same time, they go through the cell cycle together, In later studies, they also used sea urchin eggs. Large numbers of these can be obtained and fertilised simultaneously in the laboratory, after which they all go through the early cell divisions leading to formation of the embryo together. These preparations could be analysed at defined times. at which all cells would be at the same point in the cycle.

The main results from these early studies was the demonstration that some of the enzymes needed to generate the substrates for DNA synthesis were extremely sensitive to irradiation and that the resulting lack of substrate was a significant factor in blocking DNA synthesis in irradiated cells.

In the early 1960's, Margery and Lloyd again changed the direction of their research, this time to the proteins associated with DNA in the nucleus. Studies of these proteins would occupy them through until retirement and would constitute their main scientific contribution. DNA is packaged in the nucleus as chromatin, a complex in which the DNA molecules are wound around cores of proteins, the histones, in a regular repeating array, and this allows the extremely long DNA molecules to be organised to fit into the small volume of the nucleus. This arrangement not only provides a solution to a packaging problem, it is now clear that the association between DNA and histones is of major importance in cell division and the control of gene expression. The association is a dynamic one and is altered by a wide range of chemical modifications to the histone proteins. These

either directly influence the binding to DNA or alter interactions with other proteins which are involved in controlling the cell cycle and gene expression. While some of these modifications had been identified at the time when Margery and Lloyd started their experiments, their significance was not understood.

Using their regenerating liver model, Margery and Lloyd began to study one of these modifications, phosphorylation, the addition of negatively charged phosphate groups. They established that phosphorylation of two members of the histone protein family, H1 and H3, was increased at specific stages of the cell cycle and that this was extremely radiosensitive. The timing and extent of the phosphorylation was different for the two proteins, suggesting that different enzymes might be involved and they spent some time, without success, trying to identify these. However, in further experiments they also documented a range of other histone modifications which also changed during the cell cycle, suggesting that these all formed part of a much more complex system.

We now have a much greater appreciation of the significance of the extensive array of histone modifications for cell division and gene expression and this is now an extremely large and important area of research. What is clear from more recent studies is the importance of specific modifications of particular histone proteins associated with individual genes. With the experimental techniques available at the time, Margery and Lloyd were only able to look at overall global changes in these processes and the fine details, which we now know to be critically important, had to await the development of new techniques with the appropriate resolution. Nevertheless, they were among the first to appreciate the role that histone modifications might play and they performed some of the pioneering studies in this field. Margery's contribution to this research was recognised by the award of a D.Sc. in 1973.

After reaching retirement age and ceasing laboratory research, Margery and Lloyd continued for many years to go in to the department each day to the small office they had been able to retain. During this period, they embarked upon another project, one which was very close to their hearts, the compilation of a history of the Oxford Biochemistry department from its origins as a separate department from Physiology in 1920. A first edition of this history was published in 1990, with an update in 2000 and a much enlarged, final edition in 2006. As Margery's successor, it was during this period that I got to know her and Lloyd well, and I was often summoned to the office to review details in the history, particularly those relating to the Genetics Unit. These meetings often ended in much broader discussions, sometimes looking wistfully backwards to such things as the loss of Departmental libraries (Margery was the Departmental Library co-ordinator for some years), or expressing exasperation at the lack of interest in preserving historic pieces of apparatus from the early days of the department. More often they focussed on the present and the many ways in which Biochemistry was evolving, which they witnessed as they documented the range of projects in the different research groups in the Department. Of course, they were particularly keen to follow the extraordinary proliferation of studies of histone modifications and their consequences.

During this same period, Margery also wrote a short autobiography, about which you have already heard. This gives a fascinating insight into the life and work of a female scientist during the period when such women were distinctly rare. Margery was extremely proud of these accounts of the history of the Biochemistry department and her own history and rightly so as together they will continue to provide a unique way to gain an appreciation of a most remarkable woman and the world in which she lived and worked.

Dr Garry Brown

January 2020