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The first protein Structure Determinations

M. Rossmann¹

¹*Purdue University, West Lafayette, IN USA*

Max Perutz had been studying the structure of haemoglobin for 21 years using highly original and creative techniques, when I arrived in Cambridge in the summer of 1958. Most recently he had explored the use of isomorphous replacement by substituting specific amino acids with heavy metal compounds. Together with Ann Cullis, he had collected three dimensional diffraction data on native haemoglobin crystals and on three heavy atom derivatives. But now Max needed help in analyzing this data. I had had experience in determining three small aromatic hydrocarbon structures as a graduate student with J.M. Robertson at the University of Glasgow using only mechanical hand calculators, a slide rule and Beevers-Lipson strips. At the University of Minnesota, as a post doc with Bill Lipscomb, I had learned how to program one of the earliest commercial computers and solved a plant terpenoid structure in three dimensions. Thus, when I joined Max's lab, I was soon busy programming the brand new "home build" EDSAC2 computer to determine and refine the heavy atom parameters for phase determination by isomorphous replacement. When we calculated the 5.5Å resolution horse oxy haemoglobin electron density map in the summer of 1959 we were amazed to see that the two polypeptide chains of haemoglobin each had the same fold as that of myoglobin, another oxygen carrying protein determined by John Kendrew at 6Å resolution two years earlier at the Cavendish. John and his group were extending the structure of myoglobin to 2Å resolution. The high resolution map of myoglobin was calculated using my Fourier program the week after the low resolution haemoglobin map. We then saw the atomic structure of α -helices as had been predicted by Linus Pauling. Seeing evolution for the first time at a molecular level has inspired my thinking and choice of research topics ever since. In the following few years, stimulated by these discoveries, David Blow (who had returned from the US later that summer after two years of post-doc studies) and I developed the single isomorphous replacement method, the use of anomalous dispersion for phase determination, phase combination procedures and, most importantly, molecular replacement.

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