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Introductory Remarks

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The first protein crystal from which single crystal X-ray diffraction spectra were obtained was a large crystal of the proteolytic enzyme, pepsin. The experiments began, as many protein researches begin, in the laboratory of Arne Tiselius at Uppsala. John Philpot was visiting there for a period in 1934 to work with Tiselius on methods for purifying proteins: the protein he chose to operate on was pepsin. Of this he grew very large crystals—2 mm across—by accident, through leaving his preparation in the refrigerator while he was away on a skiing expedition. He showed the growing crystals to Glyn Millikan, then visiting Uppsala from Cambridge, and Millikan, knowing of Bernal's great interest in all kinds of crystals and also in biological problems, asked for, and was given, a supply to take back to Bernal in Cambridge. He carried the test-tube containing the crystals as they were, growing in their mother liquor. This enabled Bernal to observe that a single crystal shrank and lost birefringence and order on removal from its mother liquor; he therefore tried taking X-ray photographs from crystals still surrounded by their liquid of crystallization.

The diffraction effects that Bernal recorded were rich and full of detail. They showed that the crystals were ordered down to atomic dimensions and also that the repeating units were large, corresponding in order of magnitude with the molecules defined by Svedberg's measurements in the ultracentrifuge. None of the detail observed suggested, at first sight, the presence of peptide chains within the molecules and for a brief period we wondered whether they actually existed in globular proteins.

The state of general ignorance about the structure of proteins at that time is very well illustrated by the discussion meeting at the Royal Society on 'The protein molecule' which took place a few years later, almost exactly 30 years ago (*Proc. Roy. Soc. Lond.* B **127**, 1; or A **170**, 40 (1939)). Not only crystallographers were hesitant about the existence of peptide chains in globular proteins. Kai Lindestrøm-Lang gave a brief paper on globular proteins and proteolytic enzymes. In this he queried the view that the tryptic hydrolysis of synthetic peptides and globular proteins was evidence that the globular proteins contained peptide chains. He had carried out experiments which showed a temperature dependence of the protein hydrolysis which could conceivably be explained by the formation of peptide links on denaturation and before hydrolysis.

Today, through the X-ray analysis of a number of proteins, we can see that peptide chains exist and follow in detail their wandering course through molecule after molecule. For a moment, looking back, it seems marvellous that we have come so far; exactly how far we hope to learn from our present discussion.