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Fifty years of fibrous protein research: A personal retrospective

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ABSTRACT

As a result of X-ray fiber diffraction studies on fibrous proteins and crystallographic data on fragments derived from them, new experimental techniques across the biophysical and biochemical spectra, sophisticated computer modeling and refinement procedures, widespread use of bioinformatics and improved specimen preparative procedures the structures of many fibrous proteins have now been determined to at least low resolution. In so doing these structures have yielded insight into the relationship that exists between sequence and conformation and this, in turn, has led to improved methodologies for predicting structure from sequence data alone. In this personal retrospective a selection of progress made during the past 50 years is discussed in terms of events to which the author has made some contribution.

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1. Introduction

This paper charts a selection of those research developments in the field of fibrous proteins in which I have been involved and which have both excited me and stimulated me to pursue a career in structural biophysics. This is necessarily a very personal perspective and readers should view it in that light. Whether or not these contributions have been of significance is left to the reader to decide. Although the story starts in 1963 (the commencement of my PhD studies) it remains, some 50 years later, a work in progress, albeit now at a somewhat lesser degree of productivity than in my hey-day. The chance to contribute a retrospective of this type is rarely offered and I feel very privileged to have the opportunity here. By its very nature, however, I will not be able to provide as many of the details or all of the references that I would have liked to do. The reader is therefore referred to the original literature for a more complete picture as well as appropriate attribution of the work of others. I freely acknowledge that friends and colleagues from all over the world have made major contributions to the work reported here, and without their assistance and input a great deal less would have been achieved. My main aspiration in writing this paper is that readers will gain an impression of how, in my eyes, the field of fibrous proteins has been such an exciting one to be involved in over the past 50 years and, indeed, is equally likely to be in the years ahead.

2. Synthetic polypeptides and a polymer at King's College, London (1963–1966)

In 1963 I had just completed my BSc (General) in Mathematics and Physics at King's College in London and was looking for a job. I applied for a position with the British Scientific Civil Service and was successful in getting a position that would have involved me in designing ship hulls. Before I started, however, I was approached by Seweryn Chomet, a lecturer in Physics at King's College, to see whether I would like to undertake a PhD in biophysics. I had absolutely no idea what was involved and, indeed, had never even contemplated the possibility of doing postgraduate research. After some enquiries I took the plunge and signed up to work under Arthur Elliott and Maurice Wilkins. I was fortunate even at that early stage of my career in having such Supervisors. Arthur Elliott (Fig. 1a) had worked for many years on synthetic polypeptides at Courtaulds in the UK and was widely recognized for his expertise in this area. Shortly beforehand, however, Courtaulds had axed their research team in a cost-cutting measure and he was temporarily unemployed. Fortunately, King's College Biophysics Department recognized an opportunity to gain his expertise and he accepted a Readership after a 6 months sabbatical with Bruce Fraser and Tom MacRae at the CSIRO Division of Protein Chemistry in

Abbreviations: PBLG, poly-γ-benzyl-L-glutamate; IF, intermediate filament; DST, disulfosuccinimidyl-tartrate; RTT, rat tail tendon; CFDD, collagen fibril diameter distribution; PRD, plakin-repeat domain; CSIRO, Commonwealth Scientific and Industrial Research Organization; DSIR, Department of Scientific and Industrial Research; NIH, National Institutes of Health.

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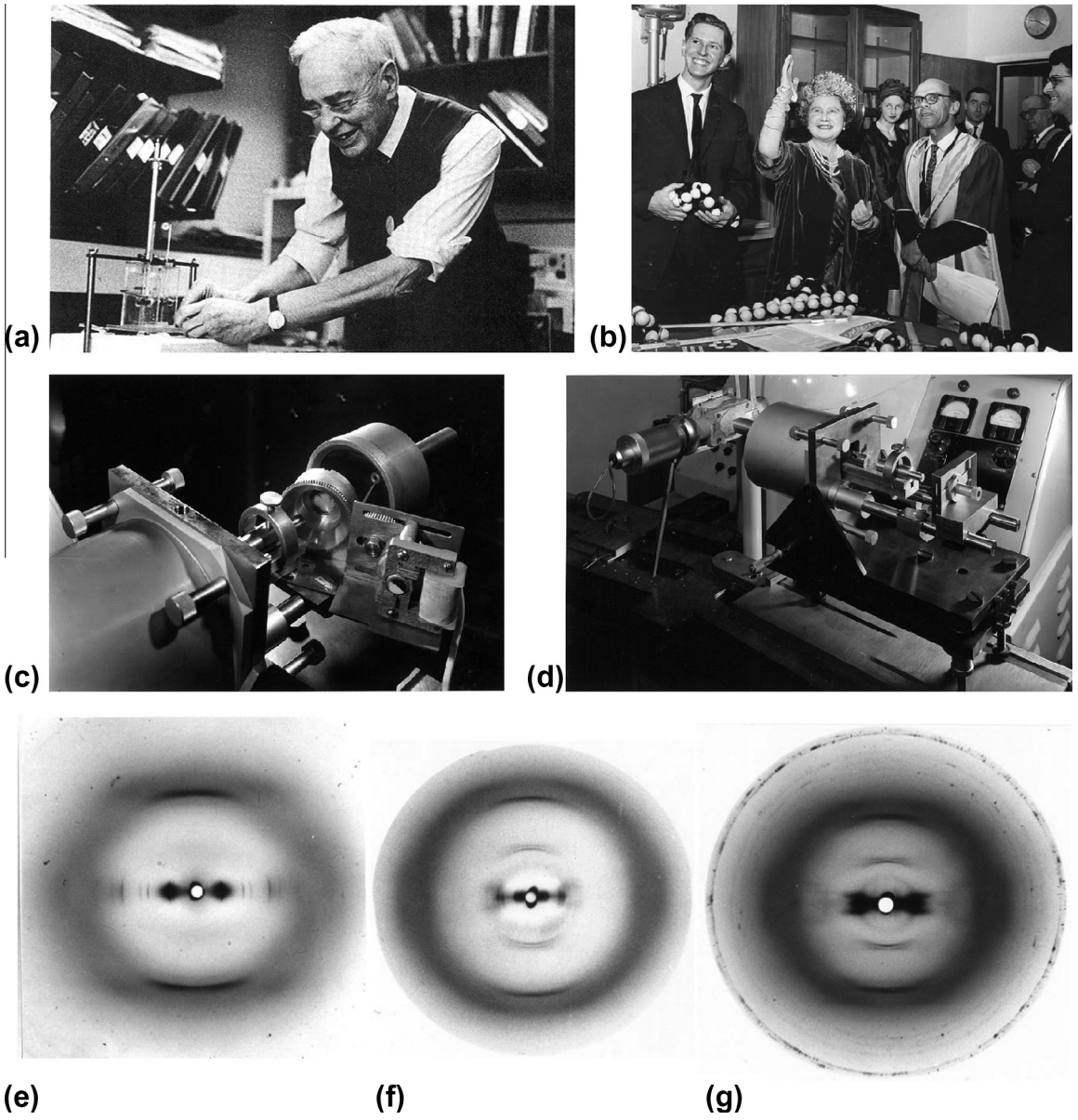

Fig.1. (a) Arthur Elliott, PhD supervisor, (b) official opening of the King's College Biophysics Laboratory in Drury Lane, early in 1964. The Chancellor of the University of London, Queen Elizabeth, The Queen Mother, was escorted by Sir John Randall, Head of the Laboratory. David Parry was the model-making postgraduate introduced to the Queen Mother. The latter is seen here waving to the girls in the Sainsbury Store hanging out of a first floor window next door, (c) toroidal focusing X-ray camera with the conical camera (at right). The orientation cell with one of its beryllium windows driven by a small motor is shown at center, (d) the same camera with a flat film holder, (e) X-ray diffraction pattern of an oriented solution of PBLG in m-cresol (38% concentration) showing features characteristic of an α-helix (and not a 3_{10} helix as had been proposed earlier by others (Luzzati et al., 1961), (f) and (g) X-ray patterns of oriented solutions of PBLG in dimethylformamide (45% and 70% concentrations, respectively) showing a weak near-equatorial layer line (f) and then a well-defined near-equatorial layer line (g) akin to that seen in the k-m-e-f group of coiled-coil α-fibrous proteins.

Melbourne. Maurice Wilkins (a New Zealander, it transpired, an attribute that would become more relevant to me later in my career than I might have expected at that time) was my other PhD supervisor. He had just been awarded the Nobel Prize with Francis Crick and James Watson for the structure of DNA. Interestingly, Bruce Fraser had worked briefly with Maurice Wilkins at King's College in the early 1950s on the structure of DNA and had produced a model that had many of the features present in the Watson–Crick structure (Fraser, 2004). The close relationship between many of the key players in the field of fibrous structures was to become a recurring theme of my career.

The Biophysics Department was in the process of packing up its equipment from its existing (underground) Wheatstone Laboratory in the Strand when I joined them. New premises had been found in Drury Lane (not far from the famous theatre) and early in 1964 Queen Elizabeth, the Queen Mother as Chancellor of the University of London, officially opened the laboratory. I was chosen to meet her as a "typical" postgraduate. I was supposed to be constructing molecular models as she strolled into the laboratory. While chatting with me she spotted a group of girls from the local Sainsbury's supermarket hanging out of a first floor room across a narrow alleyway. She waved (Fig. 1b) and the photographer snapped a picture that appeared in "The Times" newspaper and elsewhere. Suddenly I was "famous"! Reality soon set in, of course, and I spent the next month or two helping to establish the X-ray suite, painting bits and pieces and doing odd jobs round the place. Proper research commenced shortly thereafter.

My first venture involved helping to solve the structure of a polymer – polycaproamide or the γ-form of nylon 6 (Bradbury et al., 1965). Arthur Elliott had started on this problem at

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