Preface

The second half of the 20th Century saw tremendous advances in our understanding of the chemical basis of life. In this period we have gone from a time when we barely knew how amino acids were strung together to make a protein, or how genetic information was passed from generation to generation, to a time when the sequence of the human genome has been determined and the three-dimensional structures of more than 1000 different proteins, including those of several membrane proteins, have been solved. Moreover, using the now common tools of molecular biology, the amino-acid sequence of individual proteins can be engineered rationally or even evolved for new biological activities. Despite these rapid advances, we are still awaiting a full understanding of the mechanisms by which proteins adopt their folded state, and our ability to predict the structure of proteins or the consequences of mutagenesis on protein structure, stability or activity are still only limited. Research in these areas is dynamic, and exciting new insights are emerging with amazing frequency. In April 2000, the current knowledge in these areas was described and the future directions and potentials debated in the Annual Symposium of the Biochemical Society held at The University of Leeds, U.K.

Leeds University was home to Professor W.T. Astbury, FRS, one of the pioneers of the field of structural molecular biology. Indeed, Astbury first coined the term 'molecular biology' during his time in Leeds, defining it as "...not so much a technique as an approach, an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below large-scale manifestations of classical biology for the corresponding molecular plan. It is concerned particularly with the forms of biological molecules and .... is predominantly three-dimensional and structural — which does not mean, however, that it is merely a refinement of morphology — it must at the same time inquire into genesis and function" [*Nature* (1961) **190**, 1124]. As well as realising the enormous potentials of molecular biology, Astbury was also involved in the early studies of the diffraction patterns of fibrous proteins, particularly those of keratins (see front cover). Using these images, Astbury first recognized alpha to beta transitions in protein structures upon physical perturbation, a phenomenon highly relevant today in the conversion of normally soluble proteins into the toxic confomers of amyloid. It was, therefore, appropriate that a symposium entitled 'From Protein Folding to New Enzymes' that dealt with the structures of proteins, the consequences of misfolding transitions in human disease, and the engineering of structures for new functions, should have been held in Leeds.

We were delighted that many of our distinguished colleagues were able to speak at the meeting, and to share their findings with the readers of this book. The latest views of protein folding mechanisms *in vitro* and insights into some of the structural consequences of protein misfolding are described by Chris Dobson in Chapter 1. The biology of a fascinating yeast prion, as studied using techniques spanning structural biology and yeast genetics to reveal how this protein can cause the inheritance of new traits, is the subject of Chapter 3 by Tricia Serio. Ulrich Hartl and Lila Gierasch (Chapters 4 and 5 respectively) detail some of the amazing feats by which protein folding is chaperoned in cells, while Paula Booth tackles the immensely complex, but fascinating, biological and biophysical problem of how a membrane protein folds in Chapter 2. Here, both the lipid and the protein have to be considered and the reader is taken through the problems and pitfalls of working with folding membrane proteins and the insights that are beginning to emerge from this relatively untapped area.

Some of the most exciting breakthroughs in protein science today are emerging through the combination of experiment and simulations. Our ability to model proteins in action is increasing with remarkable speed, thanks to the enormous increases in computer power available today and the development of algorithms and programs that can model the folding of polypeptides and proteins. These areas are covered here in Chapters 6, 7 and 8, by Valerie Daggett, Andrew Doig and Derek Woolfson, respectively. Valerie Daggett presents the results of molecular dynamics simulations to identify and validate protein folding–unfolding transitions that agree remarkably well with experimental results. Protein design also relies heavily on input from both theory and experiment in cycles of design and redesign. The next two chapters, by Doig and Woolfson respectively, provide insights into advances in this area. Doig summarizes the factors involved in the structure, stability and folding of the α-helix, and Woolfson provides guidelines for the assembly of novel coiled-coil structures. Understanding the fundamental details of the origin of the structure and stability of relatively simple structures such as these will provide the intellectual tools that will permit us to construct new proteins in the future, and to build on the repertoire of proteins that Nature has provided. While rational engineering of enzymes can provide catalysts with altered specificities, these experiments involve often laborious step-wise modifications of existing enzyme activities. Exciting new approaches using directed evolution promise to revolutionize our ability to tailor enzymes for new functions. In Chapter 9, Mike McPherson describes the approaches of DNA shuffling and phage display, and their use in the creation of evolved protease inhibitors that hold enormous promise for the control of nematode pests. The book ends 'with a bang' as Neil Bruce describes how environmental screening has been used to produce new enzymes capable of reducing nitrate esters and their use in the degradation of explosives.

We hope that this book will provide you with an appreciation of the exciting current work in this field and its future potential. Finally, and most importantly, we thank our authors for providing the array of interesting chapters that make up this volume.

Alan Berry
Sheena E. Radford

Abbreviations

AMF	atomic force microscopy
bO	bacterio-opsin
bR	bacteriorhodopsin
CEWC	chicken egg-white cystatin
CI2	chymotrypsin inhibitor 2
CpTI	cow-pea trypsin inhibitor
DHPC	L-α-1,2-dihexanoyl phosphatidylcholine
DMPC	L-α-1,2-dimyristoyl phosphatidylcholine
DOPC	L-α-1,2-dioleoyl phosphatidylcholine
DOPE	L-α-1,2-dioleoyl phosphatidylethanolamine
DPOPC	L-α-1,2-dipalmitoleoyl phosphatidylcholine
DPOPE	L-α-1,2-dipalmitoleoyl phosphatidylethanolamine
GFP	green fluorescent protein
GTN	glycerol trinitrate
GuHCl	guanidine hydrochloride
Hip	Hsc70-interacting protein
Hop	Hsc70/Hsp90-organizing protein
Hsc	heat-shock cognate stress protein
Hsp	heat-shock protein
HSQC	heteronuclear single-quantum coherence
KIH	'knobs-into-holes'
MD	molecular dynamics
NOE	nuclear Overhauser effect
OC-I	oryzacystatin I
OC-IΔD86	OC-I lacking Asp-86
OYE	Old Yellow Enzyme
PC	phosphatidylcholine
PDB	Protein Data Bank
PE	phosphatidylethanolamine
PETN	pentaerythritol tetranitrate
PI3 kinase	phosphoinositide 3-kinase
R-gene	natural resistance gene
RMSD	root mean square deviation
SH3	Src homology 3
SPR	surface plasmon resonance
TNT	trinitrotoluene
TRiC	TCP-1 (T-complex polypeptide 1) ring complex
TSE	transmissible spongiform encephalopathy
VSG	variant surface glycoprotein