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## Preface

In an earlier volume of the Methods in Molecular Medicine series entitled *Prion Diseases* (1996), Ros Ridley and I assembled contributions from distinguished scientists in order to deliver a comprehensive protocols book that would include every aspect of prion disease research. This well-reviewed book covered human and animal prion diseases with particular emphasis on the methods used in epidemiological study of these diseases and the laboratory-based techniques for analyzing infectious material. Other volumes in the *Methods in Molecular Medicine* series described experimental protocols in such detail that competent scientists could use them to carry out similar experiments. However, because of the wide-ranging subject matter in *Prion Diseases*, and perhaps because of the hazardous nature of the experimental work, we decided to “break the rules” and not to commission a recipe book. Rather, we asked the contributors to describe their different approaches to the various problems that beset our understanding of prion diseases and, though some authors described their experimental techniques in detail, others provided a more general overview of their research.

In the *Molecular Pathology of the Prions*, I have deviated even further from the initial concept of a protocol book. I do, however, think that it follows on from the previous volume and, although the principal authors are different, many of those who contributed to *Prion Diseases* will be found among the bylines here. There is a major difference between the two books. In *Molecular Pathology of the Prions*, I have concentrated on the molecular pathogenesis of prion disease and the emphasis is on the role of prion protein. There is no mention of the epidemiology of animal and human prion diseases that figured so prominently in the earlier book. As a result of the veterinary epidemiological studies carried out by Wilesmith and his colleagues (and so well described in *Prion Diseases*), the measures put in place to curb the epidemic of BSE seem to have worked and the BSE epidemic in Great Britain is almost over. Now, concerns about BSE have been replaced by a growing fear that there will be large numbers of cases of new variant CJD as a result of the consumption of BSE-infected meat. More than 80 people have died from this form of CJD and, despite the widely varying predictions by mathematical modelers, we have no idea how many more will succumb.

There has been a major shift in the status of the prion hypothesis since that earlier volume. This hypothesis, which in its simplest manifestation says that the transmissible agent in the prion diseases is composed solely of prion protein, which has gained more widespread acceptance than it had in 1996, and its originator, Stan Prusiner (who provided the Foreword to *Prion Diseases*) was awarded the 1997 Nobel Prize for Physiology or Medicine. However, although most researchers in the field now subscribe to this hypothesis, it has become clear that in its simplest form it cannot account for all that is known about the prion diseases, and there are those who still espouse the view that the transmissible agent must comprise more than prion protein. All agree, however, that prion protein plays a key role in the molecular pathogenesis of these diseases, and the contributors to the present volume are in the front rank of those investigating this role.

In the first chapter, my colleague Ros Ridley gives an account of the way in which hypotheses develop in general and scientific consensus is constructed. She describes some of the received wisdom about prion diseases (some correct, some incorrect) and how this has influenced the development of the framework within which experimental investigation of prion disease is carried out.

Hans Kretzschmar et al. (Chapter 2) and David Brown and Ian Jones (Chapter 3) review their experiments to elucidate the normal function of prion protein and, in particular, its role as a copper-binding molecule, which acts to regulate synaptic function (Kretzschmar et al.) or cellular resistance to oxidative stress (Brown and Jones).

In Chapter 4, David Brown addresses the neuronal death that occurs in prion diseases. He offers a possible explanation derived from studies of the neurotoxicity of a synthetic peptide PrP106-126, based on the prion protein sequence, applied to tissue cultures, an explanation that incorporates a role for microglia and astrocytes.

Of major interest to prion researchers is the issue of strain of agent. One of the mainstays of the argument that the transmissible agent of prion diseases contains a nonprotein component, probably a nucleic acid, is the existence of different strains of agent. These strains are defined in terms of the regional distribution of neuropathology (the lesion profile) and the incubation period from inoculation to illness onset in defined strains of mice. Although the strain properties of an agent usually remain constant on serial passage through different animals of the same mouse strain, occasionally there is a change that results in a new strain appearing, one that has a different lesion profile and incubation time. Some argue that there has been mutation in an informational component of the agent and that the new strain has been selected. Others argue that the different strains can be encrypted by the tertiary structure of the prion protein and that

there is no evidence for an additional nucleic acid component. This discussion is not covered in this volume. However, the properties of different strains of prion disease agent are covered in Chapter 5 by Martin Groschup and colleagues, who look at the characteristics of different scrapie strains by immunochemical analysis of prion protein and in Chapter 6 by Steve DeArmond, who examines the mechanisms by which different prion strains target different brain regions.

In his experiments, Steve DeArmond made use of transgenic mice and a further three chapters are concerned with studies using such mice. In Chapter 7, Glenn Telling describes experiments in which the prion protein gene has been knocked out or replaced and which have provided information about the molecular basis of strain differences and species barriers.

In Chapter 8, Markus Glatzel and colleagues describe the use of prion gene knockout mice in conjunction with intracerebral grafts of normal brain tissue to examine the spread of infection from the periphery to the central nervous system and within the brain.

In Chapter 9, David Harris and colleagues report their studies of cultured mammalian cells (Chinese hamster ovary cells) or transgenic mice carry and express prion-disease associated prion gene mutations.

In the old literature about prion diseases it is often said that there is no immune response; indeed this has become a dogma. But recent evidence suggests that this statement is unwarranted and that there are changes in the immune system, and in Chapter 10, Samar Betmouni and Hugh Perry describe their investigations of the early inflammatory response to scrapie infection in mice and its role in the pathogenesis of disease.

In Chapter 11, Richard Greene introduces a new approach to the study of prion disease, an approach he terms electroneuropathology. Greene has applied some of the established techniques for electrophysiological recording from brain tissue slices to mice with scrapie infection and has found that changes in neuronal activity are sensitive to the combination of agent strain and mouse strain used. He has also reviewed the electrophysiology of hippocampal formation and subiculum in prion protein null mice.

Two chapters are concerned with amyloidosis. It has become clear in the past few years that many neurodegenerative diseases are associated with the accumulation of protein deposits within brain parenchyma. In these diseases a normal cellular or circulating protein is converted to an abnormal  $\beta$ -sheet form, which aggregates to form very stable, insoluble plaques or amyloid deposits. The best-known is  $\beta$ -amyloid, which is found within the plaques that are a prominent feature of the neuropathology of Alzheimer's disease. In Chapter 12, Martin Jeffrey and Jan Fraser review their work on the aggregation and

deposition of abnormal prion protein and its relation to pathological change and disease. Further they briefly discuss tubulovesicular bodies, which might have a role in the pathogenesis of prion diseases. In Chapter 13, Thomas Wisniewski and his colleagues describe their work on “ $\beta$ -sheet breaker peptides”, which interfere with the process of amyloidosis, and consider their therapeutic potential in the treatment of neurodegenerative diseases that are associated with amyloid deposition.

In the final chapter (Chapter 14) we move away from mammalian prions to consider prions of yeasts. Reed Wickner and his colleagues, who have been at the forefront of research in this area, give a full account of the nonchromosomal genes [URE3] and [PS1] of yeast that are infectious forms of Ure29 and Sup35p, and that, according to Wickner and colleagues, satisfy the criteria for being considered prions. They argue that studies of yeast prions have cast light on the biology of mammalian prions and speculate that such studies will suggest useful treatments for human prion or amyloid diseases.

This, then, is the subject matter of this volume. I am grateful to the authors who agreed to contribute, despite the heavy demands on their time and efforts in this rapidly growing and increasingly important area of biology.

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