MOLECULAR PATHOLOGY OF THE PRIONS
Edited by Harry F. Baker

The sociopolitical dimension, in addition to the unique biology of prion diseases, have resulted in a slew of books on this topic during the last 5 years, many of them concentrating on BSE and variant CJD. These have ranged widely in scope, target audience and academic rigour. However, given the current upsurge in prion disease research, and the legitimate...
interest of the specialist and non-specialist alike, there is a place, if not a need, for leaders in the field to give an overview of their recent work and to set this in context of the field as a whole.

In this regard, Molecular Pathology of the Prions can be recommended. Despite the title of the series (Methods in Molecular Medicine), the editor notes in his preface that this volume, unlike its 1996 predecessor, is not a recipe book. Instead what we get is a series of concise insights into hot topic areas of prion biology written, for the most part, by the very researchers who have pioneered the work.

There are a number of fundamental issues regarding the biology of these diseases on which a consensus is yet to be reached. This makes a comprehensive survey of scientific opinion difficult to achieve. Appropriately therefore, the volume opens with a philosophical contribution from Rosalind Ridley, a long-standing collaborator of the editor, who poses the question, ‘What would Thomas Huxley have made of the prion diseases?’. The history of the transmissible spongiform encephalopathies (TSE)/prion diseases is explored from an ostensibly Khunian perspective. Ridley charts the ‘drift’ from the viral paradigm to the heretical prion hypothesis and reminds us that ‘it is the customary fate of new truths to begin as heresies and to end as superstitions’. Bravo for that but it is also a useful reminder to the reader of the fact that one has to be rather careful picking up the terminology in this field since most of the terms are loaded with particular theoretical assumptions.

The first two scientific contributions proper, one from Hans Kretzschmar and the other from his one-time colleague David Brown, pursue a single issue, namely that of the function of the normal form of the prion protein (PrP\textsuperscript{C}) and what this might tell us about prion disease pathophysiology. The former summarizes his laboratory’s recent neurochemical and electrophysiological work, which indicates that the prion protein is a presynaptic copper binding protein in mice. This topic is extended by David Brown who summarizes his cell biology work, which he interprets as evidence for a stress-related function for the prion protein, specifically as a synaptic superoxide dismutase. The subtext of these two chapters is that a loss of prion protein function may be responsible in part for prion disease phenotype. The alternative and perhaps more conventional proposition, that prion diseases result from a toxic gain of function by the disease-associated form of the prion protein (PrP\textsuperscript{Sc}), is taken up in a second chapter, again by David Brown. This is a particularly useful chapter in that it draws together what has been learned from a series of cell biology experiments using a toxic peptide fragment of the prion protein and gives us a testable model of the degenerative process. The cell biology of the abnormal forms of the prion protein is dealt with in a later chapter by David Harris and colleagues. They have developed a powerful and remarkable series of models of inherited forms of prion disease. These models show, amongst other things, that the introduction of mutations in the prion protein gene sequence are sufficient to cause cultured cells to produce PrP with many of the properties of PrP\textsuperscript{Sc} and in transgenic mice to result in neurodegenerative disease.

The chapter by Martin Groschup and co-workers is more in keeping with the series title, in that it is a practical introduction to molecular strain typing in animal TSEs. Stephen DeArmond follows this with a chapter on selective neuronal targeting in prion diseases. This, he proposes, is a function of host–pathogen interaction defined by the composition of the glycans carried on the prion protein, and perhaps expressed by the host. Next, transgenic studies are dealt with by Glenn Telling. Much of the same material is then reiterated by Adriano Aguzzi and co-workers before they address the nominal topic of their chapter, namely neuro-invasion of the scrapie agent and what has been learned from grafting studies in mice.

What is electroneuropathology? Well it is, according to Richard Greene, a new way of examining neurodegenerative change by measurement of the effects of disease processes on primary neuronal function. This contribution was thought provoking although a little heavy going for the non-electrophysiologist. Two contributions that should be singled out for special attention are those of Betmouni and Perry and of Jeffrey and Fraser. Both are examples of clear thinking and careful morphological examination of the disease process in animals. Perry makes a strong case against the oft-repeated absence of an inflammatory response in the TSE and draws our attention to the early activation of microglia during the disease process in mouse models of scrapie. Fraser and Jeffrey on the other hand, force us to consider the ultrastructural context of the disease process and the formation of prion protein amyloid. The chapter is beautifully illustrated with a good number of immunoelectronmicrographs. The remaining two chapters cover strategies to treat Alzheimer’s and prion diseases by targeting protein conformation with β-sheet breaker peptides (Thomas Wisniewski and colleagues) and the presence of prion-like proteins in yeast (Reed Wickner and colleagues). The latter nicely returns us to the first chapter in that it forces us to consider what criteria we might use to convince ourselves that yeast proteins, that are unrelated to the prion protein, might be appropriately termed prions.

There is no doubt that this volume contains some of the very best work currently being undertaken in the field of prion disease mechanism and will give the reader a good overview of where our understanding of prion diseases currently lies and where it might be heading. Those working in the field will certainly want to have this book to hand, but they will also be aware of some of the shortcomings of the volume. According to the prion hypothesis, the structural conversion of PrP\textsuperscript{C} to PrP\textsuperscript{Sc} and possible intermediate species is central to the prion disease process, yet this topic is not tackled head on by any of the contributors. Similarly, there is little discussion of human
prion diseases here nor the emerging parallels with other neurodegenerative conditions. While the prion hypothesis may well be the new consensus, there are aspects of TSEs that are hard to accommodate within this paradigm and a dissident voice might have been a worthy addition. These comments notwithstanding, this volume is a well conceived and executed survey of the field from the modern pathobiology perspective and it is hoped that frequently consulted copies will find a place on a wide variety of personal, departmental and institutional shelves.

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