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Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects. Edited by Peter S. Harper and Max Perutz. New York: Oxford University Press, 2001. Pp. 312. \$95.00.

In March of 1993, I learned from Marcy McDonald that the gene for Huntington disease (HD) had been identified by an international collaboration of researchers. The excitement surrounding this finding was considerable, as one might expect; however, the stunning aspect of the discovery was the detection of an expanded run of the amino acid glutamine in patients affected with HD. This meant that there was a second neurodegenerative disorder caused by an expanded glutamine repeat (the first being Kennedy disease, a.k.a. spinal and bulbar muscular atrophy), and the fact that it was HD made the discovery all the more spectacular. Over the past 10 years, CAG trinucleotide-repeat expansions encoding hyperextended polyglutamine tracts have been identified as the cause of nine inherited neurodegenerative diseases. These discoveries have created an entirely new field of research that has attracted the attention of molecular biologists, model-organism geneticists, and protein biochemists, in addition to clinical neurologists and medical geneticists. The polyglutamine-repeat diseases comprise HD, Kennedy disease, six types of spinocerebellar ataxia, and an exceedingly rare disorder known as dentatorubral-pallidolusian atrophy or, in North Carolina, as Haw River syndrome.

One hallmark of the CAG–polyglutamine repeat diseases is the genetic phenomenon of anticipation, which is defined as worsening disease severity due to earlier age at onset and more-rapid progression of one's illness in succeeding generations of an affected pedigree. (Anticipation was originally described at the turn of the last century but was dismissed in the 1950s by the well-known geneticist Lionel Penrose as being caused by ascertainment bias.) Once it became clear that anticipation is a distinctive feature of the trinucleotide-repeat diseases and that the molecular explanation for anticipation is the progressive lengthening of the triplet-repeat tract as it is unstably transmitted from one generation to the next, gene identification for inherited neurological diseases greatly accelerated. By 1996, considerable progress had been made in realizing that one group of the so-called trinucleotide-repeat diseases all involved expansions of a CAG triplet tract in the coding region of the respective genes responsible for each polyglutamine disorder. With strong evidence supporting the notions that polyglutamine-expansion tracts are dominant gain-of-function mutations that cause disease by the adoption of an abnormal

structural conformation and that the disease process could be modeled in mice, Peter Harper and Max Perutz organized a Royal Society meeting to address the molecular basis of polyglutamine neurodegeneration. In 1998, this meeting brought together leading researchers from a variety of disciplines, all interested in glutamine-repeat disease. The outcome of the 1998 Royal Society meeting is a new book, entitled *Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects*.

Peter Harper and Max Perutz, who also serve as the editors of this scholarly compilation, have attempted to provide a genetic and molecular overview of the ever-expanding polyglutamine disease field. As both Dr. Harper and Dr. Perutz have played pivotal roles in the development of this field, they possess a keen appreciation of the significance of the advances presented in this work. In the glutamine-repeat diseases, an expansion of a polyglutamine tract is the causal event leading to disease pathology through a proposed “gain-of-function” mechanism. The gain-of-function property of the polyglutamine-expansion mutation is acquired when a run of glutamine residues crosses a critical length threshold and adopts a novel physical conformation. Dr. Max Perutz hypothesized that this altered structure resulted from the self-association of beta-pleated sheets of polyglutamine, a prediction that has been borne out by further investigation. How this altered structure leads to pathology is the focus of much of the work summarized in *Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects* and remains an area of intense research activity to this day. Many of the experimental studies that have led to the dominant paradigms in the polyglutamine disease field—the necessity of nuclear localization, proteolytic cleavage of polyglutamine-containing proteins, aberrant protein-protein interactions, and the phenomenology of glutamine-repeat aggregation—are described in detail, are thoroughly discussed, and are appropriately referenced.

The widely diverse nature of the polyglutamine disease field is apparent in this book. The work consists of 21 chapters written by a variety of investigators who all study the molecular basis of polyglutamine neurodegeneration (with the exception of the final chapter, which is devoted to the tauopathies and synucleinopathies, neurodegenerative disorders characterized by proteinaceous inclusions, although not glutamine expansions in these cases). After Peter Harper's brief but excellent introductory chapter that provides an overview of HD and its place within the category of polyglutamine-repeat diseases, the remaining 20 chapters are divided into five sections. The first section consists of four chapters discussing different mouse models of HD, as well as their molecular implications. A fifth chapter describes the first model of polyglutamine neurodegeneration in *Drosophila melanogaster*. The two chapters devoted to the generation and characterization of the HD R6 mouse models provide

a nice overview of this work and should serve as a useful introduction for researchers who intend to launch studies using the R6/1 or R6/2 transgenic mice developed by Gillian Bates's group. The next section consists of three chapters that provide synopses of studies aimed at understanding polyglutamine disease pathology through the identification of interacting proteins, examination of proteolytic cleavage, and analysis of protein aggregation, all done for the most part in cell culture and in vitro systems. The next four chapters comprise the third section and are similar in subject matter and scope to the second section, except that the contributors' studies are focused upon the huntingtin protein product. The fourth section attempts to address the phenomenon of genetic instability, an interesting and important feature of all the trinucleotide-repeat diseases, including disorders not caused by noncoding CAG repeats. The fifth and final section of this book is a series of six chapters dealing with a wide array of topics, ranging from the spinocerebellar ataxias and their mouse models to Kennedy disease and dentatorubral-pallidolusian atrophy to the aforementioned tauopathy/synucleinopathy chapter. The book is nicely illustrated and should be accessible to non-molecular specialists and clinical geneticists.

When considering the various contributions that comprise this volume, one does note substantial variability in terms of the style and content of the successive chapters. I particularly enjoyed the chapters that reviewed the generation and characterization of the HD transgenic mice and the first *Drosophila* model, as it was nice to find all these data collated and summarized in one place. Furthermore, these chapters struck a nice balance between presenting experimental data and providing a review/overview of the data. The cell culture and in vitro studies presented in the following chapters shift from original data publication-style papers to review-style papers, and this unevenness underscores the fact that *Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects* is the by-product of a meeting, not a preconceived or deliberate construction. The coverage given to CAG-repeat instability is rather scant by comparison to the other topics, although these chapters provide a meaningful introduction to a topic the understanding of which lags far behind others in this field. The final series of chapters make an especially nice finish to the work, even though they comprise a veritable potpourri of topics and experimental approaches. Neurologists and medical geneticists alike will find the chapter on the spinocerebellar ataxias from Drs. Worth, Brice, and Wood informative and comprehensive.

In summary, one comes away from *Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects* impressed that the contributors have authoritatively summarized an enormous wealth of data and stacks of important papers from the literature, much of which they themselves have generated. This synthesis of the state of the field in early 1999 is bound to be highly useful to graduate students, postdoctoral fellows, and clinical trainees who are being introduced to the polyglutam-

ine-repeat diseases for the first time. As one might expect from the relative importance of HD and the fact that it was the second polyglutamine-expansion mutation to be uncovered, the bulk of the emphasis of this book is placed on HD molecular research. The only problem with the work is that *Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects* provides us with a comprehensive overview of polyglutamine disease research as it was in mid-1999. In a field that is moving as rapidly as this one, researchers of glutamine-repeat diseases may find the work to be not quite up to date, as recent developments in our understanding of polyglutamine disease pathogenesis have yielded additional important paradigms that require re-evaluation of previous studies. Such a problem is not entirely unexpected, however, in the preparation of any book that deals with the pursuit of scientific knowledge. Despite the 2-year information gap, it is worthwhile to point out that certain key issues in the polyglutamine disease field, namely the role of aggregates and the basis of genetic instability, remain essentially unresolved. Importantly, the seminal studies that divide researchers on how to interpret the aggregation phenomenon are well laid out in many of the chapters in this work and therefore retain their timeliness.

In the preface to *Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects*, Drs. Harper and Perutz state that their goals for this work are "to stimulate further the already very active field, and to make it more accessible to clinicians and workers in allied areas of neuroscience" (p. xi). By presentation of a wide-ranging overview of the polyglutamine disease field, with chapters written concisely and authoritatively by leading workers in the field, I believe that these goals have been achieved. As an introduction to polyglutamine disease research, this book does a wonderful job of offering clinicians, medical geneticists, graduate students, and postdoctoral fellows a way to familiarize themselves with a rather complicated and rapidly moving field. Indeed, I can think of only one other volume—Wells and Warren's *Genetic Instabilities and Hereditary Neurological Disease*—whose subject matter overlaps with the Harper and Perutz creation, and, admittedly, that overlap is only partial. For these reasons, *Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects* is a welcome addition to my book collection.

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