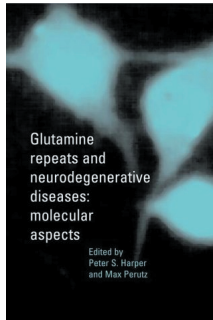


## Book Review

## Death by polyglutamine: expanding our knowledge

### Glutamine Repeats and Neurodegenerative Diseases: Molecular Aspects

edited by P.S. Harper and M. Perutz, Oxford University Press, 2001. £63.50 (312 pages) ISBN 019 850685 6



Ten years ago, polyglutamine diseases didn't exist – at least, we didn't know they were there. Five years ago, we were fully aware of their existence but had few clues to disease mechanisms.

Today, following a flurry of recent advances, we have answers to many of the mysteries underlying this class of inherited neurodegenerative diseases. We can even begin to speak of the very real possibility of therapies based on an understanding of disease mechanisms. The future looks bright for a field that didn't exist a decade ago.

Befitting this rapid advance, the field now has its own book. *Glutamine Repeats and Neurodegenerative Disease: Molecular Aspects* represents the first definitive volume addressing the molecular mechanisms of polyglutamine diseases. Based on a 1998 scientific meeting sponsored by the Royal Society and organized by the editors, this book is a collection of research-based articles by leading scientists. It is, in a sense, a celebration of scientific advances that occurred in this field in the late 1990s. These advances included both the discovery that protein misfolding is central to disease pathogenesis and the development of powerful animal models that replicate fundamental features of polyglutamine disease.

After a succinct, beautifully written introductory chapter on Huntington's disease (HD), the rest of the book is divided into five sections containing twenty chapters. The first section describes insights gained from various animal models, the second focuses on

polyglutamine aggregation and toxicity and the third covers cellular and biochemical aspects of huntingtin, the disease protein in HD. These three sections overlap considerably, but that is to be expected when much of the best science in the field crosses traditional disciplinary boundaries. The fourth section, a brief discussion of genomic features of triplet repeat instability, is peripheral to the main themes of the book. The final section covers polyglutamine diseases other than HD (the primary focus of this book) and concludes with an outstanding chapter that draws parallels between 'polyglutaminopathies' and two other classes of neurodegenerative proteinopathies, the tauopathies and synucleinopathies. Whereas some chapters are merely truncated versions of research described more completely in the primary literature, many others go well beyond the research articles upon which they are based.

What will you get from this book? In one tidy package, a fairly up-to-date snapshot of the current thinking in the field, including controversies and unresolved questions. What, for example, do nuclear inclusions of polyglutamine disease protein tell us about disease mechanisms? And how do we explain neuronal selectivity when the disease proteins are widely expressed?

What you will not get? Several currently 'hot' areas in the field are barely covered: for example, the identification of genes and compounds that suppress polyglutamine toxicity; the role of molecular chaperones in modulating disease; and the recognition that transcriptional dysregulation might be important in pathogenesis. The editors shouldn't be blamed for these omissions, however. Rather, it is a byproduct of this field's rapid progress outstripping the speed of publishing a book. Despite its minor shortcomings I am pleased to have this book on my shelf. I suspect that, on a regular basis, it will find its way off that shelf into the hands of students, postdocs or residents who want a quick overview of the field.

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## Much ado about the things we do

### The Things We Do: Using the Lessons of Bernard and Darwin to Understand the What, How, and Why of Our Behavior

by Gary Cziko, A Bradford Book, The MIT Press, Cambridge, 2000. \$37.95 (290 pages) ISBN 0 262 032775



How and why are you reading *TINS* right now? A Skinnerian view would point out that you might have read this or a similar journal before and that the outcome was

rewarding for you, for example your colleagues might have appreciated your broad knowledge base derived from reading *TINS* articles. Or you might simply enjoy new knowledge, out of curiosity. Incentives increase the frequency of the behavior, punishment decreases it. Instrumental learning is a useful model that allows making predictions about behavior and can explain proximate aspects of it. Although the power of this model might have been overestimated in the past, nobody seriously believes that the traditional divisions to conceptualize learning – habituation, instrumental and classical conditioning, and perceptual learning – are sufficient to predict and understand behavior. When respective mainstream psychology is criticized by Gary Cziko in his book, he is attacking a straw man. There is no physicist that believes that classical mechanics can provide a sufficient framework to understand the dynamics of matter – although there once might have been – and there is no psychologist who believes that instrumental learning is sufficient to understand the dynamics of behavior – although there once might have been. In both cases progress results from more elaborate and broader theories. These must encompass the earlier and more restricted model, and explain the experimental data that have supported the earlier, cruder model. Classical

mechanics can be derived from quantum theory as a fair approximation under appropriate conditions. No engineer, however, would set up a Schrödinger equation to explain the motion of a clock pendulum. In a similar manner, the pecking behavior of a pigeon in a Skinner box is well approximated by the laws of operant learning. If we want to explain different, more complex conditions, be it the scattering of two electrons or the attempts of Romeo to approach Julia, we have to broaden and change our models.

When the change has reached a certain level, when a new 'species of theories' has arrived, we might call it a revolution or a paradigmatic shift. In a way there is an evolution of theories much like the evolution of species. Cziko is right in suggesting that such a revolution in behavioral sciences is needed, and he suggests the way to proceed. However, like any revolutioner, he tends to pour the baby with the bathwater. But, don't you have to overstate the point to convince those stubborn conservatives? So let's leave the critique aside that says the author of the book would not sufficiently attempt to base his new avenues on existing roads.

Which way should the evolution of behavioral sciences go? Cziko suggests that the greatest challenge when constructing a new paradigmatic framework is already fulfilled if we take into account three lessons: (1) The Darwinian lesson, meaning to acknowledge the biological information base that all organisms are essentially born with; (2) The Bernardian\* lesson suggesting that animate behavior is determined by the purposeful control of perception; and (3) the extended Darwinian lesson, namely that the process of learning involves within-organism selection.

In particular, the Bernardian lesson, which Cziko develops into a cybernetic framework explaining aspects of behavior, is the strength of this book. Cognition is no longer the planning of responses to certain stimuli (ultimate behavior) but rather the reorganization of Bernardian perceptual control systems that control new aspects of the environment. This reorganization and the acquisition of knowledge would then follow Darwinian principles of evolution. Neither a one-way cause-effect (contingency of reinforcer – probability of behavior) logic nor a teleological intention can explain why and how you are *still* reading this *TINS* issue, whereas a

cybernetic model of a 'purposeful control of your perception' can explain what, how and why of behavior. If we can adequately specify the goal – say the intake of relevant information on the current book market – we can specify your behavior. As it gets darker during the early evening while you are reading this journal, you might switch on the light or you might use your glasses. If your children have switched on the TV you might leave the living room and go to your study – all of this behavior can be explained by having the one goal in your mind: **YOU MUST READ THOSE TINS BOOK REVIEWS!** You purposefully control your perception to fulfill this goal; you control your environment so that this purpose can be achieved (Bernardian lesson). And the ways you find to do this follows the extended Darwinian lesson: learning involves within-organism selection. But whether you steal the reading glasses of your partner or whether you go upstairs to search for your own, some aspects of behavior might well be explained by instrumental learning. The Skinnerian view is not, as supposed by Cziko, a cause-effect trap, it is the *causa efficiens* side of the coin. And already Aristotle has added the other side of the coin, the *causa finalis*, the telos, as a scientific principle to grasp the intention and purpose of behavior. For both sides of the coin, there is a wealth of data that have been adequately modeled and that must be incorporated in a broader framework. Although not elaborated in the book, the Cziko approach has the potential to achieve this. With the way the author extends Bernard's thinking, elaborating a cybernetic framework for the mind, both sides of the coin, the *causa efficiens* and the *causa finalis* are viewed within one model: they become two of many perspectives from which one can look at the dynamic self-regulatory and self-organizing system, called human.

An emphasis on these two projections might have helped to operationalize the

new theoretical framework. Insufficient clarity for experimental testing seems a major drawback of Cziko's current framework. If not testable, theories can be too good: the theory about the origin of species is one of them, as it can explain everything – think of ways to falsify it! Bringing too much Darwinian lesson into psychology includes the danger to throw us back to the time when we had a way to analyze psycho that could explain everything – post-hoc only, of course.

Much of the book is written in a popular, sometimes simplistic style making it hard for the scholarly reader to extract and accept the essential message that the author wants to transmit. The deep thoughts required by new paradigmatic ideas are often sidetracked when a reader might question some of the more trivial statements in the book. It would be very valuable if Cziko would provide a condensed version for the scientific expert readership, including the derivation of testable experimental hypotheses. Till then you will have to construct your own excerpt from the book – a task that might well be worth doing. In a time where cognitive telos is becoming mainstream fashion, the book by Cziko suggests a refreshing paradigmatic shift: if we want progress in explaining behavior, the marriage of cognitive science with cybernetics will be necessary to broaden limited cognition.

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\*Claude Bernard (1813–1878) recognized that internal processes (*Milieu interieur*) like body temperature, blood pressure or saline concentration are maintained within certain boundaries in spite of disturbing forces from inside or outside. Gary Cziko argues that living organisms not only control the internal milieu but also aspects of their external environment.

### Erratum

In the article entitled 'Multiple sclerosis: more than inflammation and demyelination' by P. Rieckmann and K.J. Smith (*TINS* 24, 435–437) we omitted to mention that this meeting was chaired by Drs Stephen Waxman (Yale University, USA) and W. Ian McDonald (Royal College of Physicians, London, UK). We apologise to the authors and readers for this error.