

Book Review

Bursting Neurons and Fading Memories: An Alternative Hypothesis of the Pathogenesis of Alzheimer's Disease, by Michael R. D'Andrea, Academic Press, 2014, 170 p., ISBN: 978-0-12-801979-5

Reviewing this book is a challenge. It does not fit easily into modern categories of scientific literature but would not have been out of place in the late 18th and 19th centuries when scientific monographs were more the rule than the exception. The overall thrust of the book centers on work spanning almost two decades, mostly conducted by the author and his collaborators, that provides the foundation for “an alternative hypothesis” underlying the pathology of Alzheimer's disease (AD). Of course, proposing an “alternative” implies the existence of another hypothesis, which, as the author rightly notes, has come to be accepted almost dogmatically. In this case, it is the “amyloid cascade hypothesis”, of which there are several variants but all based on the idea of extracellular accumulation of amyloid peptides, some of which are neurotoxic.

The vast majority of the evidence presented by Dr. D'Andrea, and his corresponding argument, is based on meticulous histological and immunohistochemical studies of sections of postmortem brain tissue from AD victims as well as non-demented “healthy” individuals. The central claim is that amyloid (the A β ₄₂ peptide, in particular) is taken up by neurons and causes their degeneration from the “inside-out” rather than by extracellular neurotoxicity. The evidence is quite convincing, at least to me, that this amyloid peptide occurs intraneuronally and should be considered a suspect based on its being in the right place at the right time.

The book provides beautiful photomicrographs that provide clear examples of the phenomena of interest ranging from artifact-free staining of intraneuronal A β ₄₂ to triple-stained sections demonstrating the spatial organization of plaques containing amyloid, astrocytes, and microglia. Anyone wishing a clear description of the essential findings and the resulting hypothesis without having to consult the primary

research papers will find their wish fully granted here. The writing is clear, the editing careful, and the references sufficient to show the way to the most relevant literature.

Reading this book reminded me in many ways of the monographs of Ramon y Cajal, which were also primarily based on microscopic observations of nervous tissue primarily stained with a single method (the Golgi stain). Whether the hypotheses proposed by D'Andrea will end up being correct, as were so many of Cajal's, only the future can answer. But opportunities to explore the development of a hypothesis through the eyes of a dedicated scientist have become rare indeed and can be especially helpful to younger people just coming into the profession, whether or not they have a specific interest in AD research. The methodical approach described here, including the careful attention to possible sources of artifacts, is a realistic portrayal of the hard work required both in the laboratory and at the microscope. (A minor distraction is the use of the singular first person throughout the book, which implies minimal contributions from his published co-authors.)

So why is reviewing this book such a challenge? Primarily because, in spite of my recommendation of the potential benefit to the young scientist, it is not obvious to whom this book will otherwise appeal. The current “leaders” in AD research? Unlikely. Having worked for a few years in the AD field myself, I can sympathize and agree with Dr. D'Andrea's view that the field continues to be dominated, in terms of resources and attention, by the reigning hypothesis. In fact, I was one of the organizers of the conference in Cincinnati that he mentions in the book where he was invited to participate in debating alternative hypotheses pertaining to AD. We organized three such conferences over a period of 5 years and the attendees found them to be stimulating and worthwhile. However, as far as I can tell, they have had minimal impact on the subsequent focus of research and/or funding priorities in the field of AD research.

All that said, there is little evidence to indicate that those who currently control the purse strings, or even the establishment of research priorities, will have any

interest in reading this book. Their minds were made up long ago and who wants to call into question the foundation on which many careers have been built? One might alternatively wish that the book would be of help to the families who have been stricken with the disease and hoping for guidance, either to help their loved ones or minimize the risk of the disease for themselves. But the level of technical detail in this book, while not overwhelming, will still be beyond the reach of most interested laymen.

The individuals one would most hope would read this book are those who establish overall research policy in this field but whose livelihood does not directly depend on promoting a particular hypothesis. Unfortunately, in my opinion, the current state of policy-making in this area is structured in a way that makes it virtually impossible for such individuals to gain access to alternative views. The science is complex and the scientific establishment is entrenched. Navigating the burgeoning literature has become impossible for any individual scientist and one's best hope for a career in this environment is to sign on to a "successful" laboratory pursuing the dominant hypothesis where resources continue to be funneled. There simply is no reward for bucking the trend, in spite of the lip service occasionally given to the goal of pursuing new directions. If and when that changes, there

will be an obvious readership for books like this. One can only hope that that time will come sooner rather than later spurred on, at least in part, by the continued failure of clinical trials based on the reigning dogma.

In spite of the foregoing, I do not want to end on a negative note. Dr. D'Andrea and the publisher are to be commended for taking on the task of clearly presenting the path of discovery that led him to his novel interpretation of the role of amyloid in AD. On a purely scientific level, I think his hypothesis needs to be fortified in some areas and does not adequately address some of the major pathological features of the disease, e.g., the regional distribution of plaques and their relationship to tangles. However, that is the nature of all hypotheses, especially those formed to account for a disease as complex as this one. What is clear from this book is his commitment to the scientific enterprise and I applaud him for completing this project. Perhaps the fact that such a book exists at all is its own justification. And perhaps, at some point in the future, a young scientist will take it up and seriously consider the alternatives proposed therein. Maybe he or she will burst onto the scene with novel insights and the current dominant hypothesis will itself be a fading memory.

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