Toward a holistic model of Alzheimer'sHow Not to Study a Disease

Alzheimer's Research – Debacle or scientific triumph?

Most people have been touched by Alzheimer's disease, the most common cause of dementia. Over 30 million people worldwide are living with Alzheimer's and numbers are growing as our population ages. These staggering numbers and the devastating nature of the disease have pushed research for effective treatments. Over the past three decades, the research field has been dominated by the amyloid cascade hypothesis – the idea that accumulation of amyloid beta in the brain kicks off a chain of events involving clumping of tau protein in tangles and massive neuron death that causes dementia. In his new book aimed at the general public, Prof Karl Herrup presents a scathing critique of the amyloid cascade hypothesis and the effect this hypothesis has on research. He describes this hypothesis as "a bully" preventing other avenues of research including a personal experience of when an advisory committee member said to him "Son, if you're not studying amyloid, you're not studying Alzheimer's."

Herrup evocatively summarizes the fear and the personal and societal devastation caused by Alzheimer's disease. He presents an engaging history of the field and unfolding of the amyloid cascade hypothesis then puts forward three "inflations" in the definition of Alzheimer's disease linking it to amyloid. The first starts with Alzheimer and Kraepelin who linked plaque and tangle accumulation in the brain to dementia symptoms in a single patient, Auguste D. They published this new disease in a textbook in 1910, which Herrup argues gave undue weight to linking pathology to disease. This is substantiated by the presence of amyloid and small amounts of tau in the brains of some healthy elderly people. However, the presence of both pathologies in the characteristic "Alzheimer's" pattern with amyloid throughout the brain and tau pathology that extends beyond the medial temporal lobe is almost never observed without dementia symptoms. One can argue that the pathologies do not cause the dementia but they are undeniably present in the over 60% of people with dementia who we currently define as having Alzheimer's disease. Throughout the book the focus on dementia being caused "by amyloid" often glosses over the very important distinction that Alzheimer's disease has requisite tau pathology in specific regional patterns in the brain. There are not many scientists left who would argue that amyloid alone is sufficient to cause dementia.

The second inflation hinges on the politics of how Alzheimer's research is funded in the US via the National Institute of Aging (NIA). There is a very interesting description of the early years of the NIA including political manoeuvring using Alzheimer's disease and the emerging data showing plaques and tangles in the brains of most people with dementia to leverage funding from the aging politicians who control the budget. This section is very well argued and interesting, albeit very US-centric, but it implies that there has been too much funding for Alzheimer's research. When compared to other biomedical fields, dementia lags far behind in funding for example there was 6 times less dementia research funding than cancer research funding in the UK reported in 2012 (*4*).

The third inflation comes from the 2011 revision of the diagnostic criteria for Alzheimer's which include amyloid biomarkers and defining a preclinical phase of disease. While Herrup rightly points out that the presence of plaques alone does not mean a person is on the path

to Alzheimer's dementia, these revised criteria also included biomarkers of neurodegeneration, tau, and functional changes as well as including tau in the preclinical definition, which is much more likely to reflect a dementing disease rather than harmless age-related plaque accumulation.

Herrup proposes a holistic model of Alzheimer's pathogenesis that encourages research into the contributions of all cell types in the brain. This is a convincing and well-supported strategy that has been put forward by several scientists over the past 5 years (*1*, *2*). However, there is also a less convincing assertion that we should return to the definition of Alzheimer's disease solely based on dementia symptoms. Different patterns of brain atrophy and different pathological lesions can result in clinically similar "dementias". This can be of vital importance clinically for example in the choice of drugs to treat patients. The use of classic antipsychotics is beneficial for Alzheimer's symptoms but is dangerous in dementia with Lewy Bodies as they exacerbate Parkinsonism symptoms and can cause neuroleptic malignant syndrome (*3*).

The harsh light this book shines on the amyloid hypothesis shows some of the humanity of scientists and our motivations such as increasing profits in the pharmaceutical industry and increasing academic funding, but it does not delve very deeply into some of the important underlying motivations in academic science which also affect progress in the field such as the drive to publish novel positive, dramatic results over incremental solid work.

Since this book was written, the first disease-modifying drug for Alzheimer's disease, aducanumab, which clears amyloid beta from the brain, has been approved by the FDA (*5*). Unfortunately, this "success" is not likely to change Prof Herrup's view on the amyloid cascade hypothesis. If you think the amyloid cascade hypothesis is controversial, just wait until you read about this anti-amyloid drug approval. Some of the road to this approval is covered in Herrup's book, and I'm sure many more critiques will be coming soon.

Despite the controversies highlighted in this book of our "stubborn backward-looking field," The past decades have not been a complete debacle in studying this disease. There has been remarkable progress in what Herrup elegantly points out is an inordinately complex disease of our complex, remarkable brains. While we may not have triumphed over the disease yet, the broadening of research avenues suggested in this book and by many others in the field are likely to result in life changing treatments for dementias.

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3. I. Yunusa, A. Alsumali, A. E. Garba, Q. R. Regestein, T. Eguale, Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. *JAMA Network Open*. **2**, e190828 (2019).

4. R. Luengo-Fernandez, J. Leal, A. Gray, UK research spend in 2008 and 2012: comparing stroke, cancer, coronary heart disease and dementia. *BMJ Open*. **5**, e006648 (2015).

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