

## Book Review

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# Of Synuclein and Other Demons

**Synuclein and the Coelacanth: The Molecular and Evolutionary Origins of Parkinson's Disease** by James M. Gruschus, Academic Press, 2021, 312 pp.

Pre-press 13 August 2021

For several generations of neurologists, the protein alpha-synuclein has been at the center of the Parkinson's disease universe. Because of a nearly mythical stature, a historical profile of this ubiquitous string of 140 amino acids was long overdue. Dr. James Gruschus account from the benches fills that gap, merging encyclopedic knowledge on the pathology, molecular biology, and genetics of synuclein—with an evolutionary prism, and he promises, “wild flights of theorizing and speculation.”

The ichthyology reference to the coelacanth, a fish considered a living fossil, seems a double barrier to entry: synuclein and coelacanth do not summon inviting imagery even in the mind of discerning readers. While heavily referenced, as it is fitting for a subject matter with a robust line of research, the nearly 300 pages are surprisingly readable. They reveal a narrative strung with well-digested influential publications, sprinkled with self-deprecating humor. While liberally deploying methodological jargon, there is a welcome effort to render tools and themes accessible to an audience beyond those directly engaged in the basic science and clinical research of ‘synucleinopathies.’

The promise of “wild flights of theorizing and speculation,” however enticing, may be exaggerated. The book sanctions the same age-old chronicle of alpha-synuclein aggregation as the chief villain in the drama of neurodegeneration. The story starts promisingly with the observation that alpha-synuclein has been conserved since prehistoric genomes,

beginning as far back as the coelacanth, further protected by the deliberate redundancy of beta- and gamma-synuclein. But not even the admission that “a function of a protein molecule typically depends on its assuming the correct shape” brings the reader to reckon with the consequences of losing alpha-synuclein in its normal state. If alpha-synuclein is an evolutionarily preserved and redundant protein, wouldn't the adoption of an “incorrectly shaped” beta-sheet aggregate be consequential by preventing it from functioning? Disappointingly, Gruschus only tangentially touches on the biological consequences of this loss of protein function. He devotes most of his efforts to painting the standard portrait of alpha-synuclein in the neurological literature: once aggregated, it must turn toxic.

The pivotal event in such argument, he contends, was the discovery in 1997 that the Contursi kindred of autosomal dominant Parkinson's disease was caused by an *SNCA* point mutation in its 53rd amino acid. The assumption that it was a gain rather than a loss of function was cemented in 2003 when alpha-synuclein was demonstrated to be “overexpressed” in patients with *SNCA* duplication and triplication. These observations were shaped into dogma after the elegant work of Braak and colleagues in under 50 Parkinson's disease brains: alpha-synuclein aggregates in a stereotypical pattern, appearing ostensibly first in the peripheral nervous system, later in the central nervous system. Cross-sectional data were interpreted dynamically: proteins actively *move* from

one area to another. Further, such pathology was necessary and sufficient to create symptoms and drive the process of neurodegeneration. Lewy pathology was not just a consequence of trouble, it was its very source. Correlation and causation became forever conflated.

Since the story of alpha-synuclein is built around its assumed toxicity when aggregated, much of what unfolds in *Synuclein and the Coelacanth* is peppered with “unusual,” “curious,” and “surprising” qualifiers, as the corresponding loss of normal synuclein is either invisible or implicitly deemed inconsequential. For instance, Gruschus notes that knocking out alpha-synuclein in young mice makes no difference and in fact protects them from the effects of MPTP, a mitochondrial toxin. “Surprisingly,” aged knockout mice do develop deficits (age is a major risk for Parkinson’s disease). Halfway through the book, we learned of experiments in which alpha-synuclein overexpression stimulates the clearance of mitochondria by mitophagy, which served to postulate that Parkinson’s disease may be caused by reduced numbers of mitochondria. Yet studies using fluorescent labeled antibodies on brain tissue led to “another surprising result: the axons and presynaptic boutons of Parkinson’s patients had more mitochondria than in controls and Alzheimer’s patients!” In chapter 8, it is noted that “one of the curious things about Lewy bodies” is that the proportion of Lewy pathology-containing substantia nigra neurons stays relatively constant regardless of how many neurons have already been lost. Gruschus offered two explanations, both at odds with the notion of alpha-synuclein toxicity he supports: “[either] the neuron loss rate is constant and Lewy bodies form toward the end of the neuron’s life [or] Lewy bodies form during only a relatively brief period shortly after onset of the disease.”

Two thirds of the way into the book, in a restoration of its coelacanth spirit, this question is formulated: “... the synucleins had to be important! Why else had they been so conserved for hundreds of millions of years?” Gruschus preemptively suggested some answers to his own question just one paragraph apart: “This, in fact, is one of the central debates addressed in this book. Are mutant alpha-synuclein molecules somehow toxic to neurons in and of themselves, or do the mutations somehow lead to higher levels of alpha-synuclein in neurons? Is it the higher level of alpha-synuclein, normal or mutated, which ultimately leads to Parkinson’s disease?”

How could this important question not prompt an answer that in any way relates to the significance of

losing that which was evolutionarily conserved? Why does it embrace the uncertainty of any toxic function gained, overlooking the certainty of normal protein function lost? *Did evolutionary forces preserve this protein and rendered it redundant to increase the odds of toxicity to neurons or to mitigate their depletion in a brain under biological stress?*

The book invests the remaining two thirds of its pages summarizing the wealth of data supporting the contention that Parkinson’s disease is “a kind of hybrid with prion aspects” whose symptoms may be the “result of differing fibrils morphology or other factors present in the purified fibrils.” Gruschus endorses the observation from experiments in laboratory animals that alpha-synuclein pathology “travels to the brain” from the gut, lungs, or nose, as per the Braak staging scheme, “which accurately describes most nongenetically related Parkinson’s disease” (in fact, many exceptions have been reported). He never directly considers the possibility that as alpha-synuclein becomes aggregated, its normal pool depletes, bringing with it a loss of its normal function.

Some allusions to the loss of alpha-synuclein function seem to appear by accident. For example, the A30P alpha-synuclein knock-in mice “made the protein so nonfunctional that it was similar to having no alpha-synuclein at all” (page 62). “Our tricky protein is something of a paradox. Experiments suggest that synucleins have roles in recruiting proteins to synaptic vesicles and moderating the release of their neurotransmitter cargo” (page 85). Autopsy studies showing extensive pathology in the brains of people without obvious symptoms during life “led some authors to propose an alternate hypothesis that alpha-synuclein amyloid [...] could actually have some sort of protective role” (page 106). Returning to the theme of evolution, Gruschus writes: “If ramping up alpha-synuclein revs up mitochondrial activity, and this is a big if, maybe humans evolved higher alpha-synuclein levels to help mitochondria in nonmyelinated projection neurons provide the extra energy needed to maintain longer axons” (page 187). On the observation that the appendix contains high levels of alpha-synuclein, Gruschus does not consider the possibility that the aggregation could be in reaction to certain bacterial strains but cursorily wondered, “Could it be that alpha-synuclein has some role in immune function in the appendix?” (page 212).

By the end of Chapter 6, Gruschus makes the following admirable assertion: “a likelier possibility is

that Lewy pathology is a relatively benign side effect of whatever true neurotoxic agent is in Parkinson's disease, and that the neurotoxicity can vary from person to person based on genetics and particular environments." For a moment I thought Gruschus was about to introduce the concept that Parkinson's disease encompasses many subtypes, each with different underlying biology. Wishful thinking. Stories of generalized toxicity followed on Chapter 7 (MPTP toxicity) and 8 (oligomeric toxicity).

A homemade laboratory in California concocted a synthetic heroin, which included MPTP, toxic to the zona compacta of the substantia nigra and rendered *frozen* six addicts. MPTP has since served as the most popular animal model of Parkinson's disease—never mind that those from whom it was discovered developed an acute clinical syndrome that no expert clinician would have diagnosed as Parkinson's disease today. Separately, neuropathology laboratories contrived "oligomeric toxicity." If alpha-synuclein is not toxic in its normal configuration nor when it is aggregated into Lewy bodies, a gain-of-function premise for 'proteinopathies' can still be defended by blaming that which lies in-between: oligomers—even if there is no consensus on what this fleeting species looks like. Gruschus, in fact, struggles here. He writes, "the biggest issue is the heterogeneity of their structures from a homogenous solution of amyloid peptide monomers, a veritable zoo of oligomers could form, some in minutes, others in hours or even days . . . sizes ranging from a few monomers to a several dozen." It is hard to accept the intellectual whiplash that normal monomeric peptides can turn into toxic oligomeric peptides, and then, upon turning into Lewy bodies, become non-toxic again. Thus, oligomers are conceived as the elusive and ephemeral "toxic" protein station between two far more stable, non-toxic protein states.

There are other cognitive acrobatics keeping the arbitrary rule of oligomeric toxicity from falling apart. One is that many oligomers do not turn into fibrils, so they must be "off-pathway oligomers." Another is that while alpha-synuclein fibrils injected into mice trigger the spread of pathology from the injection site, the injection of alpha-synuclein oligomers do so far less, "despite evidence that oligomers are the more neurotoxic form." Yet another is that in patients with recessive *parkin* mutations, there is little or no evidence of Lewy pathology, suggesting that the disease can appear "even in the absence of alpha-synuclein oligomers." So much for that.

Altogether, the book suffers from the unavoidable internal inconsistencies that come from the convenient but unrealistic single-disease model of Parkinson's disease, where each discovery is considered a piece in a unifying puzzle. It is therefore no accident that Chapter 14 is titled "Seeking a Magic Bullet." It provides homage to the unending pursuit of *a* biomarker of disease progression and *a* treatment to slow the progression in everyone affected, disregarding their biological heterogeneity. A brief review of the history of negative trials, and a glimpse into newer molecules, concludes with the standard "Parkinson's disease may be closer to getting its magic bullet." Gruschus does not dare to envision a different forest from the many "curious" trees he described. None of the many "surprising" findings fed "wild flights of theorizing and speculation" about the way Parkinson's disease has been conceived. The century-old clinicopathologic paradigm of Parkinson's disease, it seems, need no changes, and synuclein will one day be defeated.

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## DISCLOSURES

Dr. Espay has received grant support from the NIH and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, Neuroderm, Neurocrine, Amneal, Adamas, Acadia, Acorda, InTrance, Sunovion, Lundbeck, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from USWorldMeds, Acadia, Sunovion, the American Academy of Neurology, and the Movement Disorders Society. He is cofounder of REGAIN Therapeutics, owner of a provisional patent on compositions and methods for treatment and/or prophylaxis of proteinopathies.