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Alberto Espay , Benjamin Stecher
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Brain Fables

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The Hidden History of Neurodegenerative Diseases and a Blueprint to Conquer Them

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Every effort has been made in preparing this book to provide accurate and up-to-date information that is in accord with accepted standards and practice at the time of publication. Although case histories are drawn from actual cases, every effort has been made to disguise the identities of the individuals involved. Nevertheless, the authors, editors, and publishers can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors, and publishers therefore disclaim all liability for direct or consequential damages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.

For everyone living with a neurodegenerative disorder, for their caregivers and for the advocacy groups working to build a better tomorrow.

And for all those at the bedside and in the laboratory reconfiguring the war against brain aging and fine tuning its weaponry.

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Preface 1 – The Question

Three years ago, the patriarch of a Cincinnati-based philanthropic foundation and patient of mine living with Parkinson's disease approached me with a question: If I had unlimited funding, how would I change the way we study and treat Parkinson's disease?

This was an unusual request. All funding for research is limited, which restricts the scope of the questions we can ask. As a practicing physician and clinical researcher, I have been trained to look for the most efficient way to answer whatever question I am investigating. This is the hypothesis-driven method of scientific inquiry, which allows us to answer small problems in a defined period of time with a finite set of resources. It also dictates that experiments should be based on accumulated data and on predictions of what might reasonably happen to a phenomenon or behavior after a given intervention. This is an important hinge around which medical science revolves. All experiments to date have been artifacts of funding restrictions in medical research and a homage to the idea that "fishing expeditions" are not good science. We *should know* what we are looking for.

For the last 15 years, neurologists working to answer questions about Parkinson's disease have lived in two different, mutually exclusive universes. Beginning in 2004,[1] we began accepting that Parkinson's disease may be an umbrella term for a spectrum of disorders, each with different symptoms, range of severity, and varying responses to treatments. The other universe is shaped by our belief that those variations are part of the same disease. Despite all the differences we see in our patients, we can target the disease as if it were one phenomenon. By searching for common threads, we tell ourselves, we will one day discover one or two biomarkers[1] that capture the complex biology of Parkinson's disease – and use them to develop therapies to slow disease progression in everyone with the disease.

At about the time of the philanthropist's request, a dear colleague and friend from Buenos Aires, Dr. Emilia Gatto, invited me to give a lecture she titled "Revision of the definition of Parkinson disease" for a symposium sponsored by the Pan-American Section of the International Parkinson and Movement Disorders Society, in March 2015. Just before, the Society's Task Force on the Definition of Parkinson's Disease had released revised criteria for diagnosing Parkinson's.[2] Emilia asked me to discuss the differences between the new and old versions of the clinical criteria for Parkinson's disease, but also encouraged me to critically assess the extent to which the changes would enable us to develop better symptomatic strategies and test new therapies to slow disease progression.

As I prepared the lecture on the "Redefinition of Parkinson's criteria" and thought more about the question posed by my patient, I found myself working on two parallel tracks that were not converging. What if our understanding of Parkinson's disease is also impeding our ability to find cures? Could it be that generating hypotheses based on what we think we know, along with our rigid funding models, is making it nearly impossible to find what we really need to know? After all, many of the most important scientific discoveries have come

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[1] Biomarkers are any measurable indication of the presence or severity of a particular disease. One of the best examples is the monitoring of blood-glucose levels in diabetics. Development of biomarkers are critical for the development of new and improved therapies.

from dogged examination of the unknown, without preconceived hypotheses or restrictive lines of questioning.

This led me to perform a review of the data we were collecting in an ongoing biomarker development program funded by the Michael J. Fox Foundation called the Parkinson's Progression Markers Initiative (PPMI). This is the largest and most expensive study ever attempted to uncover biomarkers of Parkinson's disease. That analysis, as we will discuss in the book, led us to question the very foundations of this and similar programs.[3] By mid 2018, with two papers published, and a third on the way, challenging a central tenet of Parkinson's and Alzheimer's diseases (the causal role of aggregates of protein, alpha-synuclein in the case of Parkinson's and beta-amyloid and tau in the case of Alzheimer's),[4] I decided to reach out beyond my circle of neurologists. I contacted a *New York Times* journalist who had just published the article, "Scientists Racing to Cure Alzheimer's." That piece fit within the classic story line: undesirable proteins fill the brain of Parkinson's and Alzheimer's, and many treatments to clean them up are just within reach. In an email, I asked her if she would be interested in writing about "the other side." She replied, tersely: "Thanks for writing. You make a powerful case for biomarkers, but it is not clear that there are good biomarkers yet for Parkinson's disease. So, it does not seem to be a story for us at this time."

That statement became the spark that set this book in motion. She was correct, I had no biomarkers to trumpet. What I failed to convey to her was that the reason we had no biomarkers, and the way we were looking for them, *was the story*.

Neurodegenerative diseases do not exist. All are labels neurologists created before we had the insight and tools needed to accurately define them. So long as we cling to them, we will never find what we are looking for.

Time has come to put an end to these fables.

Alberto J. Espay, MD, MSc, FAAN

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Preface 2 – Enter Patient

At roughly the same time that Alberto was approached by his patient philanthropist in Cincinnati with the question that would lead him to want to write this book, I was on the other side of the planet coming to grips with a similar conundrum.

In November 2013, I was diagnosed with Parkinson's disease. I was a 29-year-old kid doing quite well for myself as a managing director of an education company in Shanghai when I got the news.

I didn't know anything about the disease at the time. I had no family history of Parkinson's, and I hadn't even heard of anyone with it outside of Muhammed Ali and Michael J. Fox. I went and found a clip of Ali lighting the torch at the 1996 Summer Olympics in Atlanta and intently watched his quivering hands as he lit that giant flame. Most people probably look at that moment as a defiant act of courage from this great man who had conquered the world and not let anything stop him from getting what he wanted out of life; not Joe Frazier, not the United States Government, and not Parkinson's disease. But what I saw when I looked back at that film was the future I was now doomed to live: hands trembling, frozen expression on my face, barely able to walk properly, probably reliant on a myriad of different pills just to make an appearance.

It's not easy figuring out how to move on with life as a young man faced with that kind of fate. Our healthcare systems aren't much help. Patients typically get 20 minutes every six months with their neurologist, just enough time to go through an awkward series of motor tests and questions that supposedly say something important about our disease before a prescription is written and token words of encouragement exchanged.

So where to go? Who to talk to? At any other time in history there would be nothing that anyone on Earth could do. But we live in remarkable times, I soon realized I had more resources at my disposal than any king or emperor had ever dreamed.

To the Internet I went. There I found people all over the world working diligently to fix what was ailing me. It was strange and confusing at first. The last biology class I took was in tenth grade, but over time I got used to the vocabulary and started being able to make sense of the papers I was reading. I soon found myself enthralled by the puzzle that is the human brain and why certain parts of it degenerate faster in some than others.

Before long, just reading the papers was not enough. I wanted to know what was happening at the bleeding edge of research, what was in the pipeline, and what I could do to help speed things up. As my symptoms progressed, I also became keenly aware that this puzzle was going to be too important to me to simply leave to others to figure out.

Which brings me to that moment in time three years ago when, as Alberto was toiling with how to reconcile the request from his patient benefactor with the newfound understanding he was developing about the search for biomarkers, I decided to leave my career in China behind and dive head first into this field for an accelerated course of study.

I have since spent my time touring some of the top biomedical labs on the planet and meeting with hundreds of the best physicians and scientists in the field. (And, as any good millennial would, I started a website (tmrwedition.com) where, as of this writing, I have interviewed over 80 world experts on the subject.)

Parkinson's sucks, but I wouldn't trade these last few years for anything. The information age and this disease have gotten my foot in the door into places I would otherwise never have been. It also gave me the chance to observe science in action as it pushes forward a frontier of knowledge. I have learned more along the way about the brain, biology, and disease than I ever thought possible. However, I have also learned that medical science is not quite what I thought it was.

For most of my life I was a passive consumer of science. I'd read a few articles and popular science books here and there, and generally took as gospel most of what was acknowledged to be scientific consensus. From the outside, science looks like the ultimate storehouse of credibility from which all that we know about the world emerges fully formed. However, for the last few years I have have been able to enter that house and browse the section labeled "Neurology and Neuroscience – Subsection: Parkinsonisms." At first glance it appeared relatively neat and tidy. But having now read through many of its volumes, and having met most of its living authors (and even contributed a few pages myself), I see that many of its volumes have been filled by narratives we created that might be blurring our ability to distinguish truth from fiction, slowing us down in our attempts to effectively treat these diseases.

I now find myself in a rather unique position. On the one hand, I'm a patient patiently waiting for new therapies to come online. On the other, I also now get flown around the world to attend meetings and conferences about this disease and share my insight into what we should be doing next.

The question that now drives me, which I think is fundamentally the same one Alberto faces, is how to do the most good with this position I find myself in? What direction should we be going in? How can I leverage my influence to accelerate the development of better therapies for myself, for the 7 million to 10 million others around the world living with this condition, and the millions more yet to be diagnosed?

For me, this book is an attempt to answer that question, to lay out some of the most important lessons I have learned from all the people I have interacted with along the way, and to help shed some light on a new way of thinking which I believe may be our best hope to one day finally putting an end to degenerative brain diseases.

Benjamin Stecher

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Special Thanks from Benjamin Stecher

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