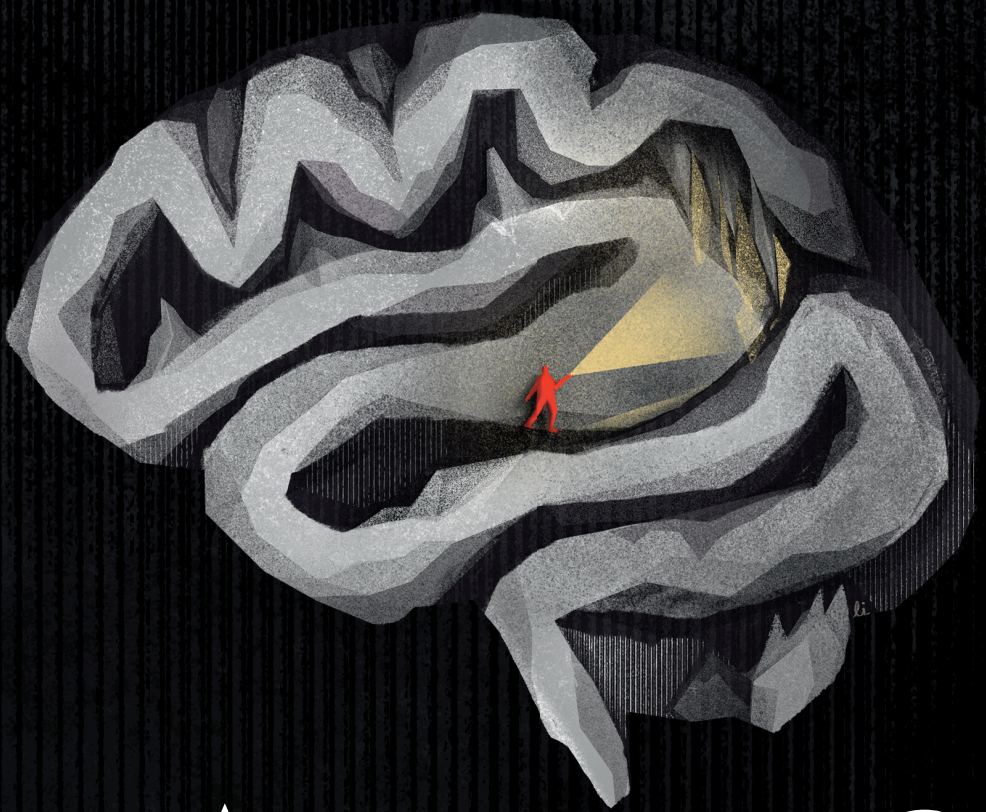
Alberto Espay • Benjamin Stecher

BRAIN FABLES



THE HIDDEN HISTORY OF NEURODEGENERATIVE DISEASES AND A BLUEPRINT TO CONQUER THEM

From Chapter 1, The Shaky Six and the "Second Reality"

The model we use for diagnosing neurodegenerative diseases, such as Parkinson's and Alzheimer's, was shaped by combining descriptions of symptoms, such as slowness or forgetfulness, with a forensic approach to understanding the nature of these symptoms. This fallacy has been largely driven by a belief that what brains look like after death can explain the range of what they experience during life.

From Chapter 2, Pieces of *a puzzle*?

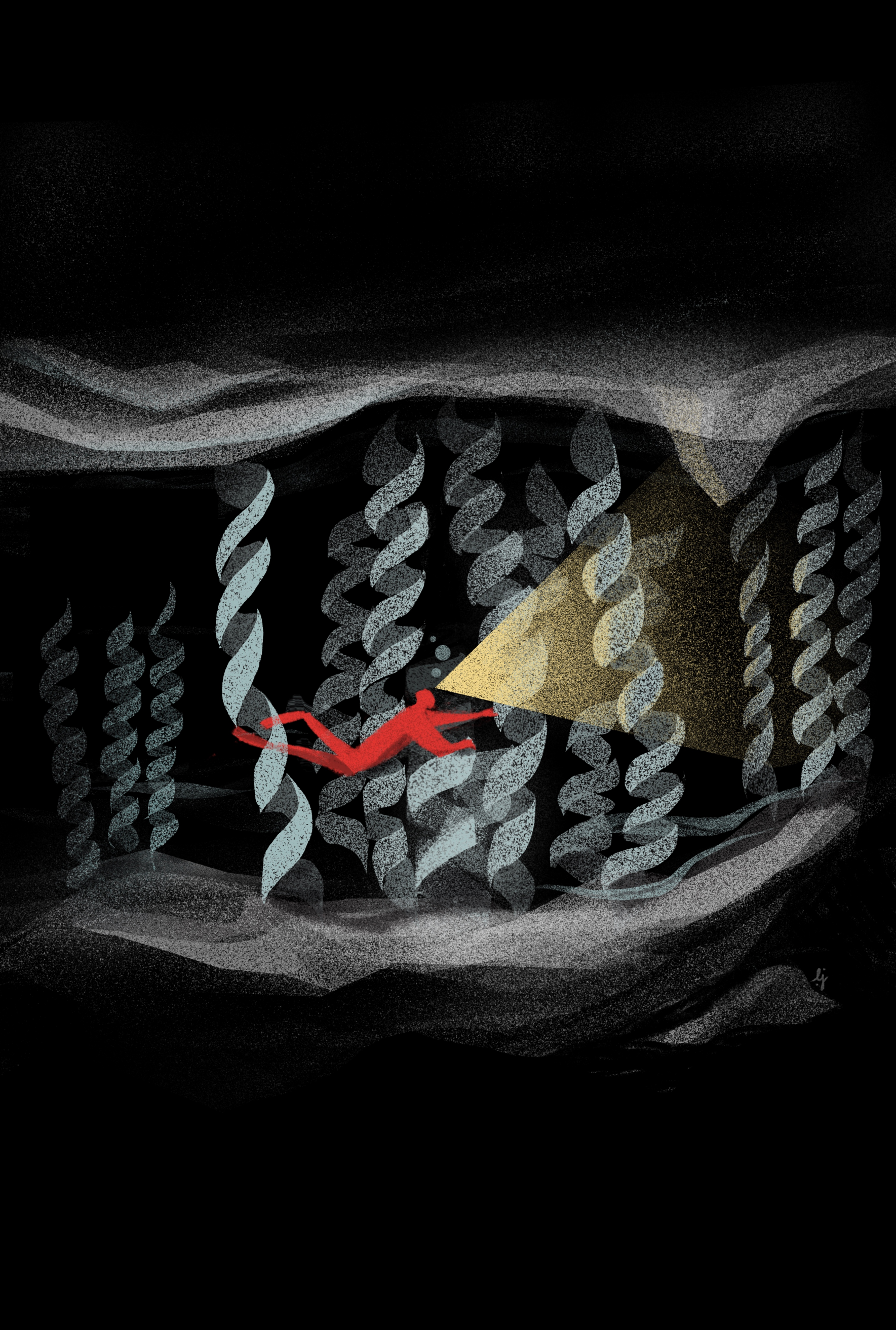
If a patient who had slowness, stiffness, and tremor is discovered at autopsy to have certain proteins, which pathologists call **Lewy bodies**, the diagnosis of Parkinson's disease can be definitively confirmed. Because these proteins are very common, people with an ever-growing range of clinical manifestations that suggest a diagnosis of Parkinson's during life are confirmed to indeed have Parkinson's after death.

From Chapter 3, Disease "Redefinition" – A Tough Pill to Swallow

Discoveries of genetic mutations in people with symptoms of Parkinson's, or who at death were discovered to have the same proteins of those known to accumulate in Parkinson's, have informed the idea of a wide, increasingly complex disease. As if each of these discoveries is a piece of the same puzzle.

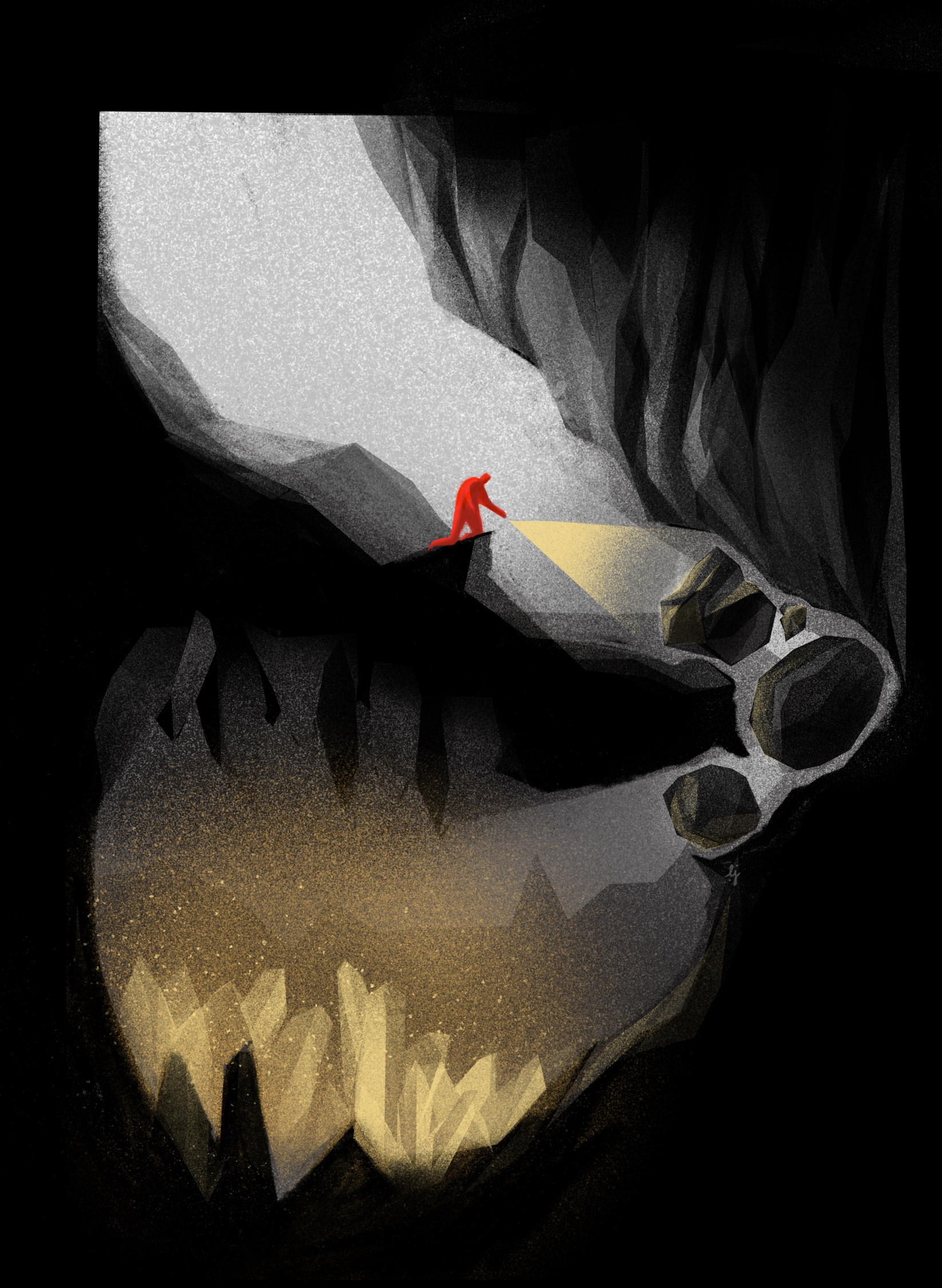
From Chapter 4, Disease Subtypes: The Promise and the Fallacy

Patients may express a disease with many different symptoms. Some may have mostly tremor. Others difficulty walking. Yet others suffer from cognitive more than motor difficulties. Despite dividing patients into **clinical subtypes**, the brain shows the same patterns of protein accumulation when examined at autopsy.



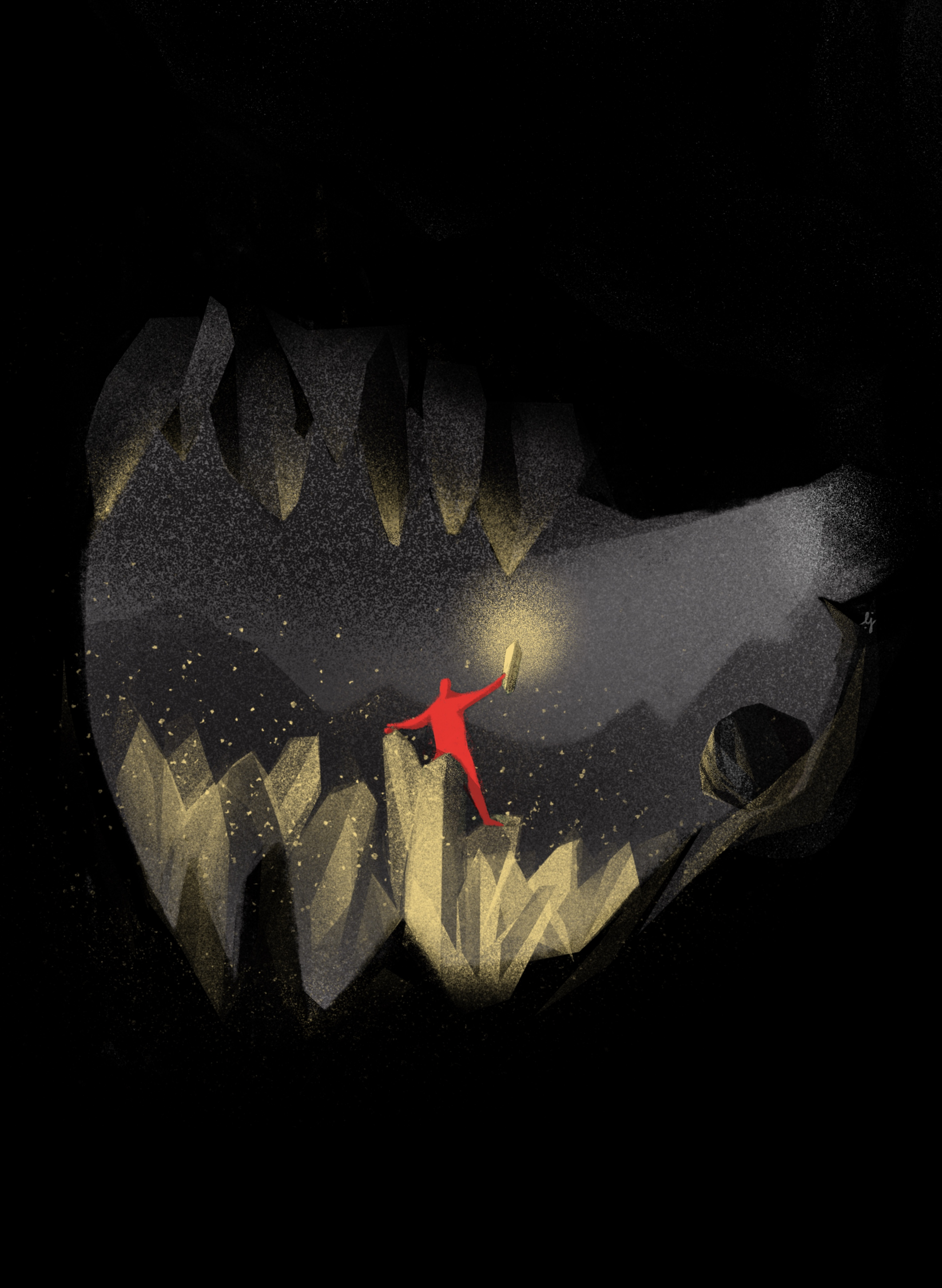
From Chapter 5, Protein Paradox

The type of brain proteins found during brain autopsy determine how neurodegenerative diseases are classified. For instance, if the **alpha-synuclein** protein accumulates into **Lewy bodies**, the disease is called Parkinson's. If the **amyloid** protein clumps into **plaques** and **tau** protein into **tangles**, the disease is called Alzheimer's. But too many patients with Parkinson's have amyloid and too many with Alzheimer's have alpha-synuclein. In fact, pure amyloid in Alzheimer's disease is the exception, not the rule; as is the case with pure alpha-synuclein in Parkinson's.



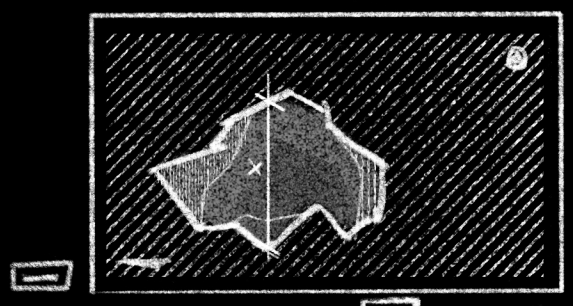
From Chapter 6, The Fault in Our Models

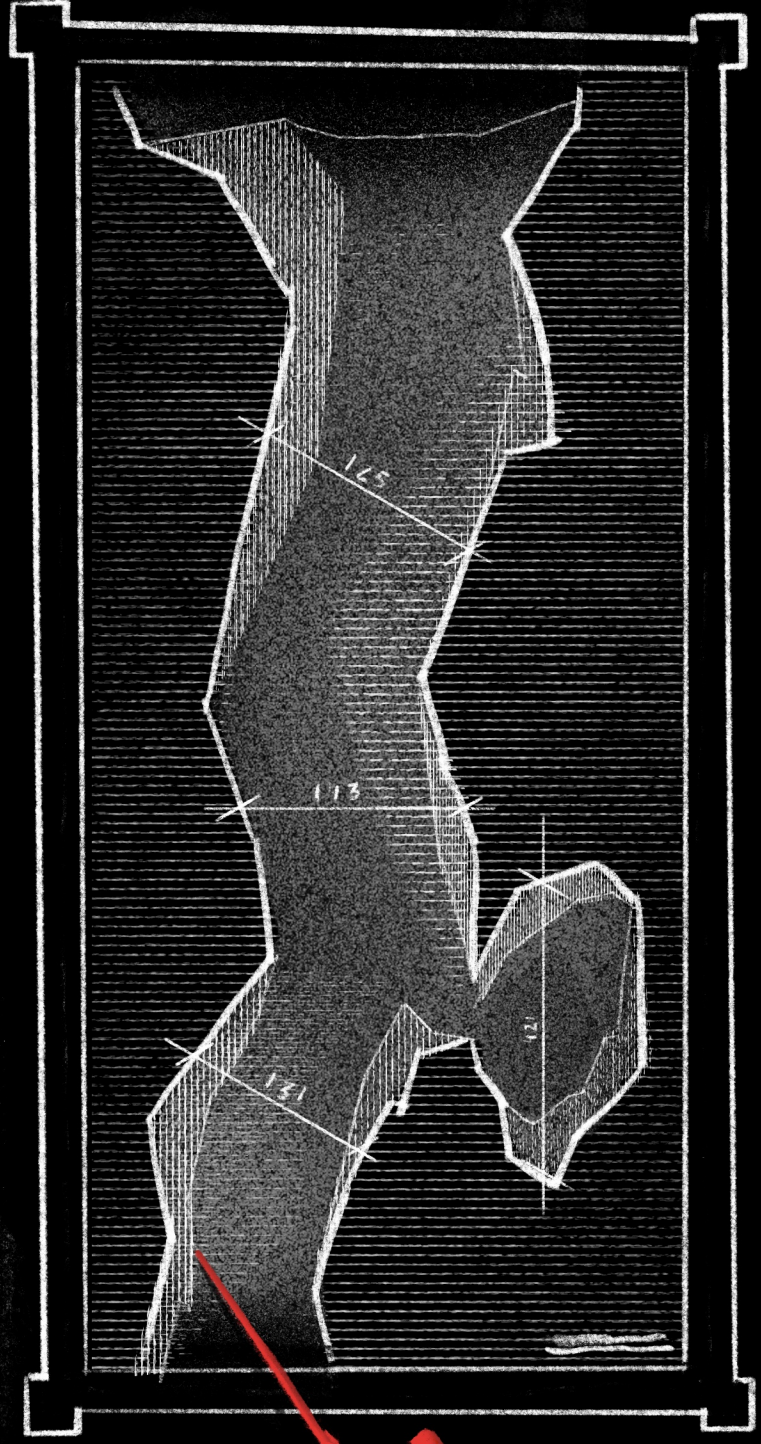
Is a patient with Parkinson's expected to develop Alzheimer's 8 times out 10? Or might it be that a biological abnormality threatening the brain's health also triggers the accumulation of proteins that, by virtue of our forensic approach to knowledge, get to be classified as separate diseases? This is why diseases of the brain are also referred to as proteinopathies.



From Chapter 7, Biomarkers: The promise and the fallacy

The end in the word “proteinopathy” comes from the suffix “pathos”, derived from Greek to mean “suffering or disease”. By defining Parkinson’s disease as an alpha-synuclein **proteinopathy**, or **synucleinopathy**, we imply the disease is caused by the accumulation of that protein, alpha-synuclein. Similarly, by defining Alzheimer’s as an **amyloidopathy**, we blame amyloid accumulation as its cause. If we can measure alpha-synuclein, we can use it to indicate the presence of Parkinson’s –that is, a Parkinson’s biomarker. A test that measures beta-amyloid is recognized as a biomarker of Alzheimer’s.

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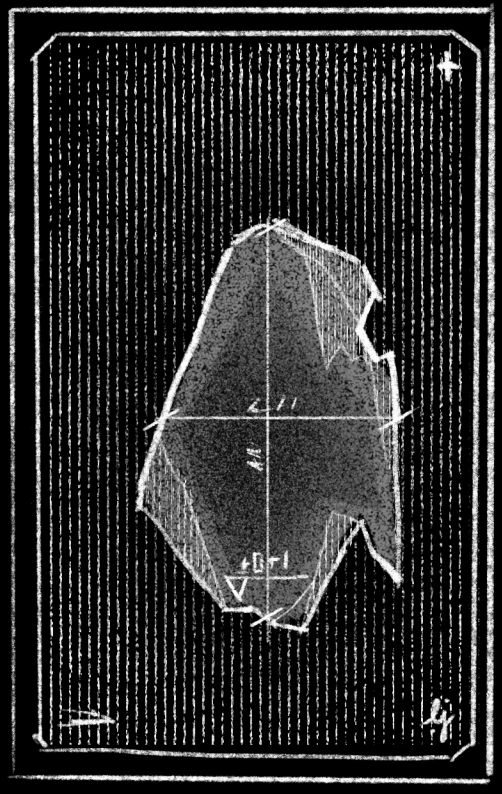
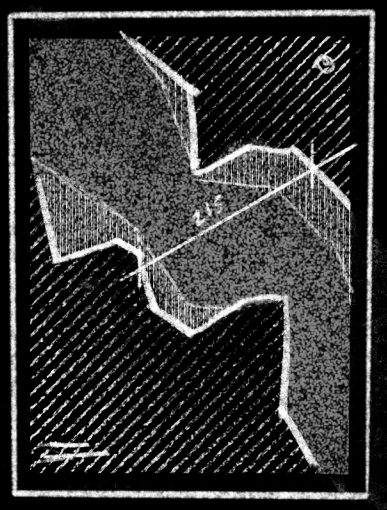
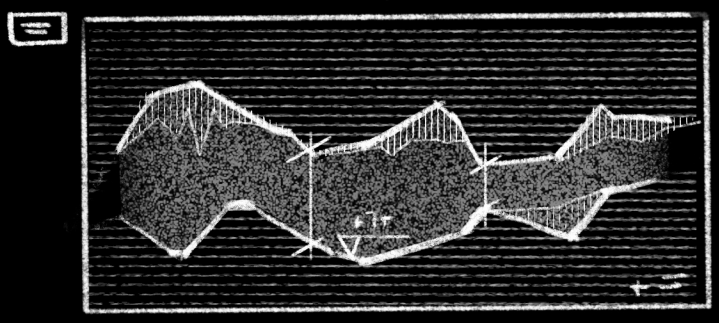






From Chapter 8, Lessons from Oncology

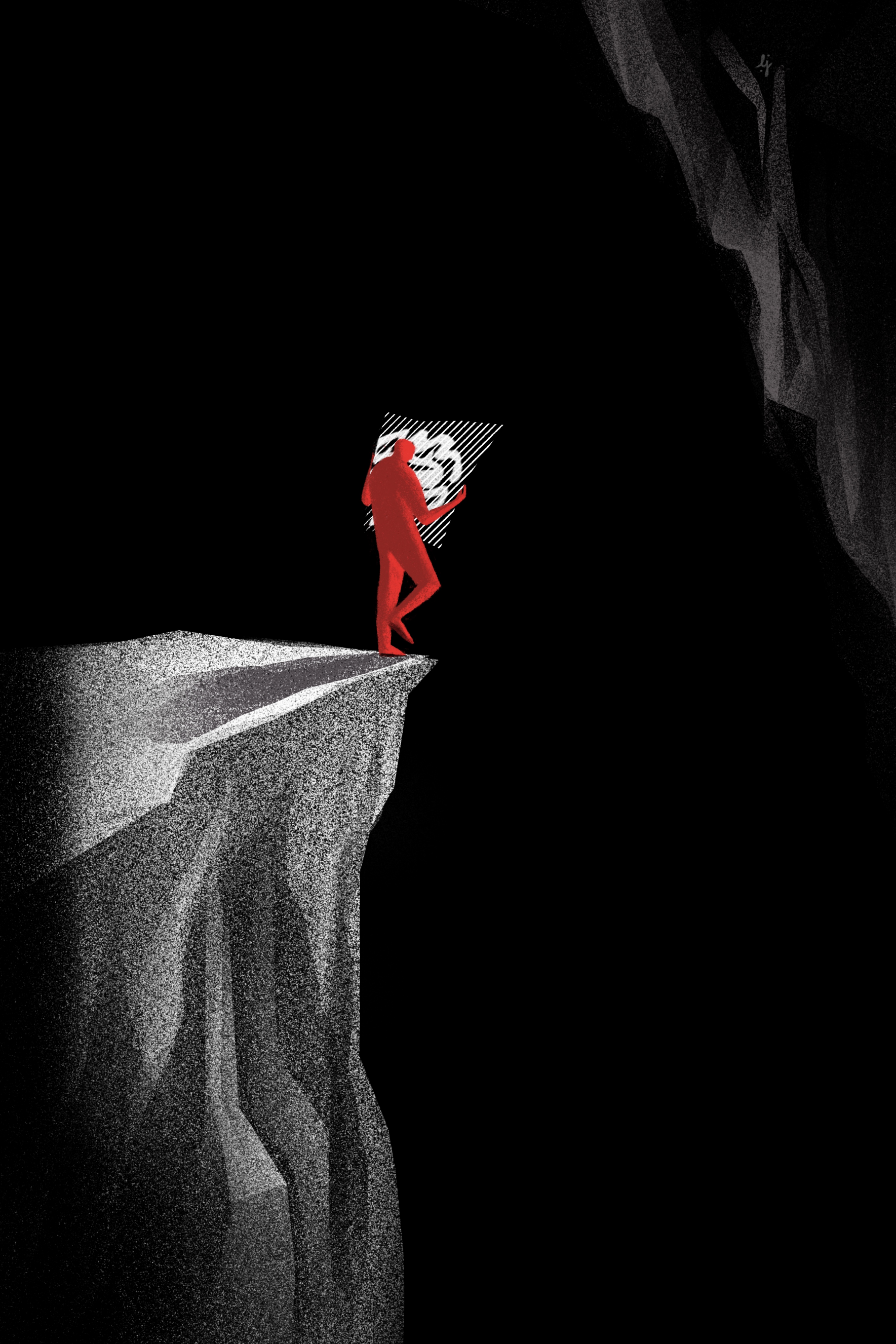
In other fields of medicine, diseases are a collection of related but distinct biological entities, each with their own set of biomarkers and treatments. Because no medication has been capable of slowing everyone with a disease, but only some subtypes within it, the lessons from other fields is to parse out Parkinson's, Alzheimer's and other diseases of brain aging into biological subtypes, each also with its own set of biomarkers and treatments.

From Chapter 9, Symptomatic vs. Disease-Modifying Therapies

While improving symptoms of a disease can be achieved by rectifying common denominators (e.g., treatments increasing brain dopamine to correct the dopamine deficiency of everyone with Parkinson's), slowing the disease itself cannot apply the same approach. Treatments to slow down progression can only work by targeting the biological abnormalities present in the individual treated but absent in most others even if sharing "the same disease." Biomarkers validated for a global disease but not for individuals with a disease will not serve to properly tailor therapies to individuals likely to respond.

From Chapter 10, The hypothesis that refuses to die

But in Alzheimer's and Parkinson's diseases, we have used the same approach to treat symptoms and to slow disease progression. In Alzheimer's disease, disease-modifying strategies have been invariably applied to one common denominator: amyloid. To date, all 35 clinical trials of anti-amyloid treatments have made no difference or worsen patients. The hypothesis that amyloid aggregation causes Alzheimer's disease remains alive despite overwhelming evidence to the contrary.

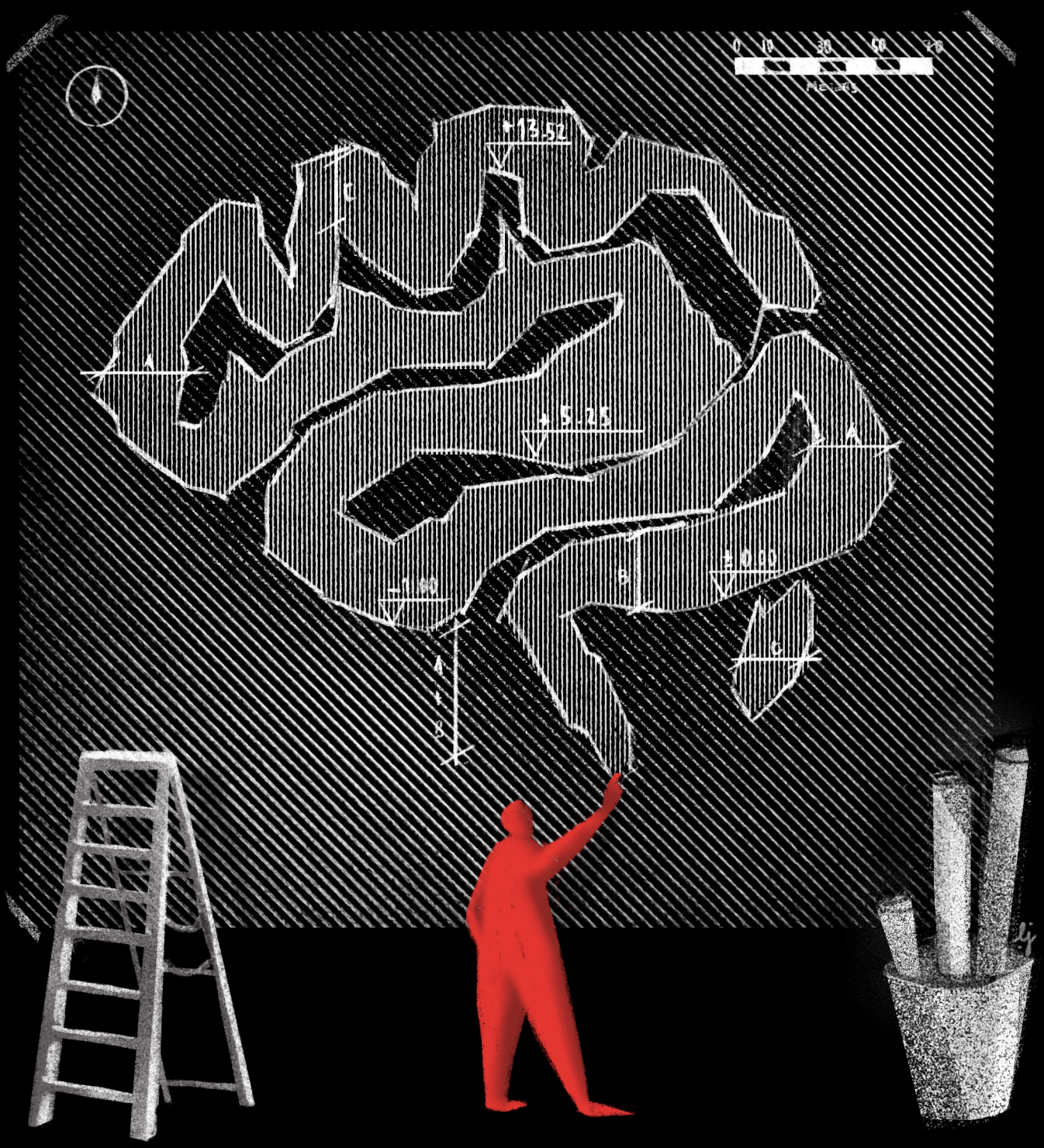


From Chapter 11, Our Living Dissonance

This is our living cognitive dissonance: Parkinson's disease is a collection of many diseases but we are close to finding a single, unifying biomarker, based on the protein alpha-synuclein, and a single, unifying treatment, based on destroying alpha-synuclein. We live with the hope of curing a disease with many causes.

From Chapter 12, The Scientific and Lay Narratives

The protein-based definition of diseases created a powerful narrative. If they emerge when proteins aggregate in the brain, we could measure these proteins even before symptoms appear. This is now possible by measuring beta-amyloid in normal individuals directly in the brain using a PET imaging technique or in the fluid that bathes the brain. These data show that over 60% of 85-year-olds have high amyloid in their brains yet only 10% of them have dementia. Should we hold on to the narrative that they are in the “Alzheimer’s spectrum”?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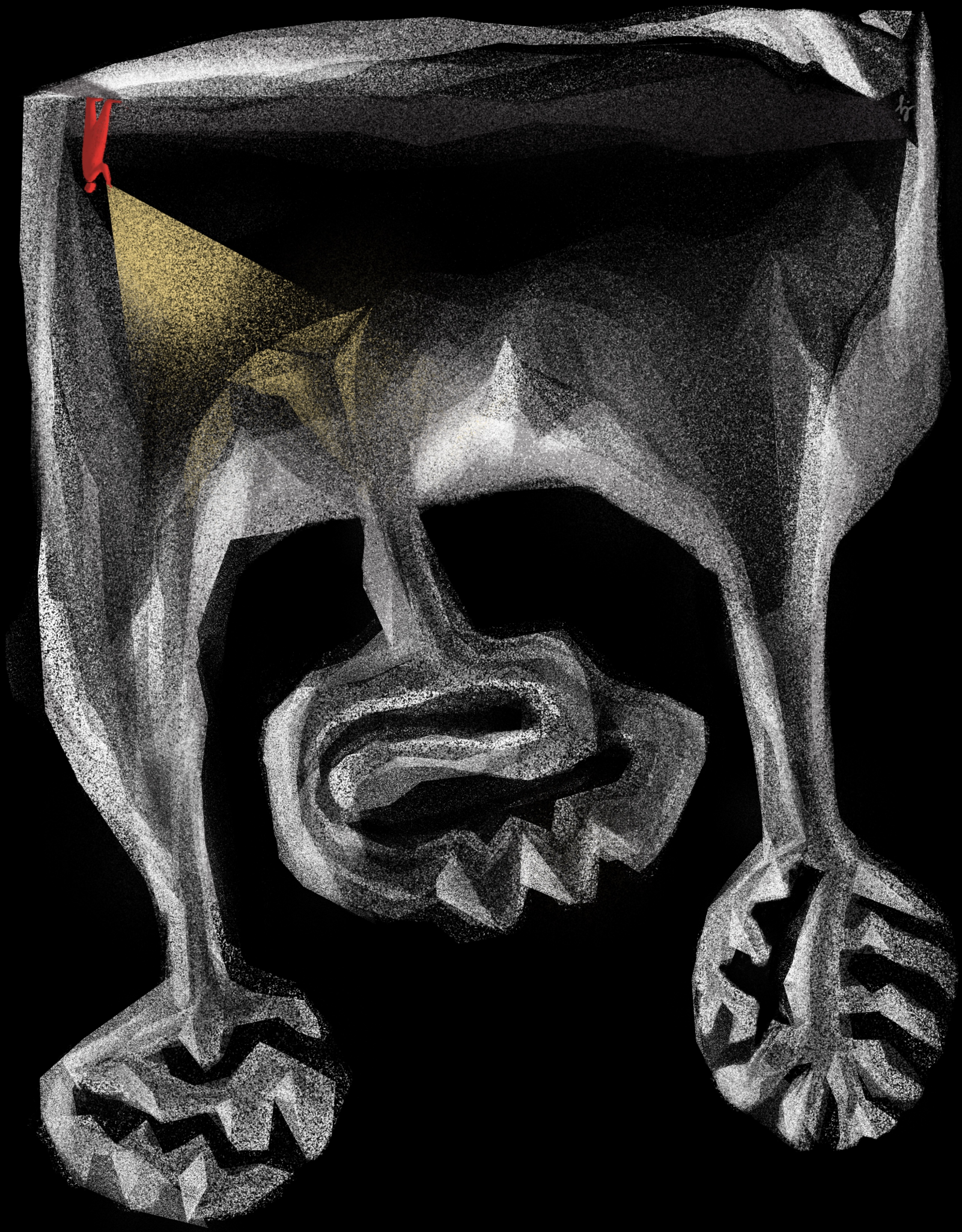
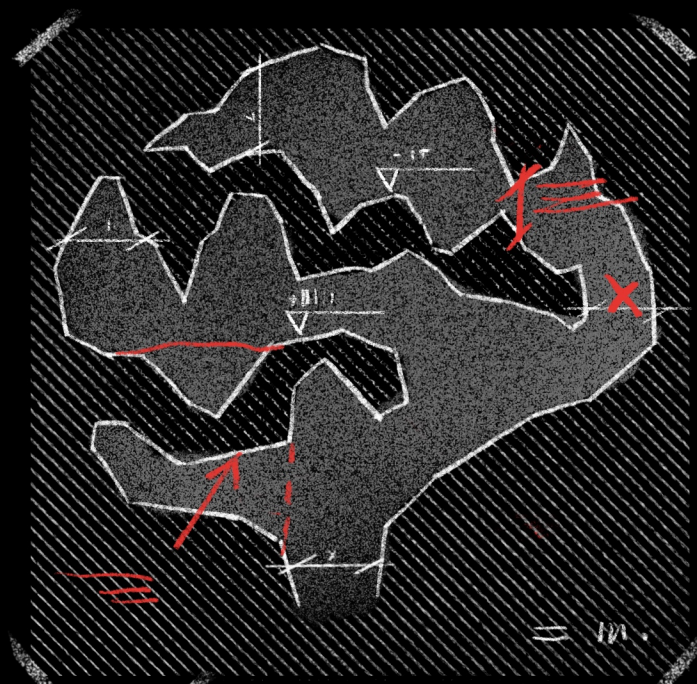
From Chapter 13, Challenges Viewed from Afar

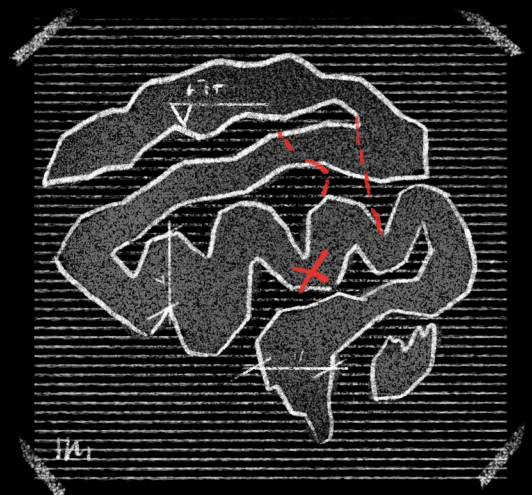
It is becoming clear that a perfect model of Parkinson's or Alzheimer's will not capture the unique manifestations of individuals with these diseases. The blueprint for conquering these diseases will require studying the many pathways where normal aging can detour into abnormal aging in different individuals – even with the "same disease" as we currently define them.

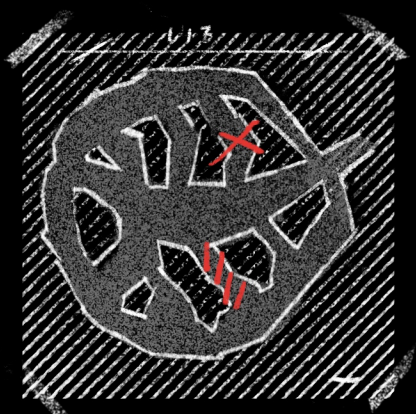


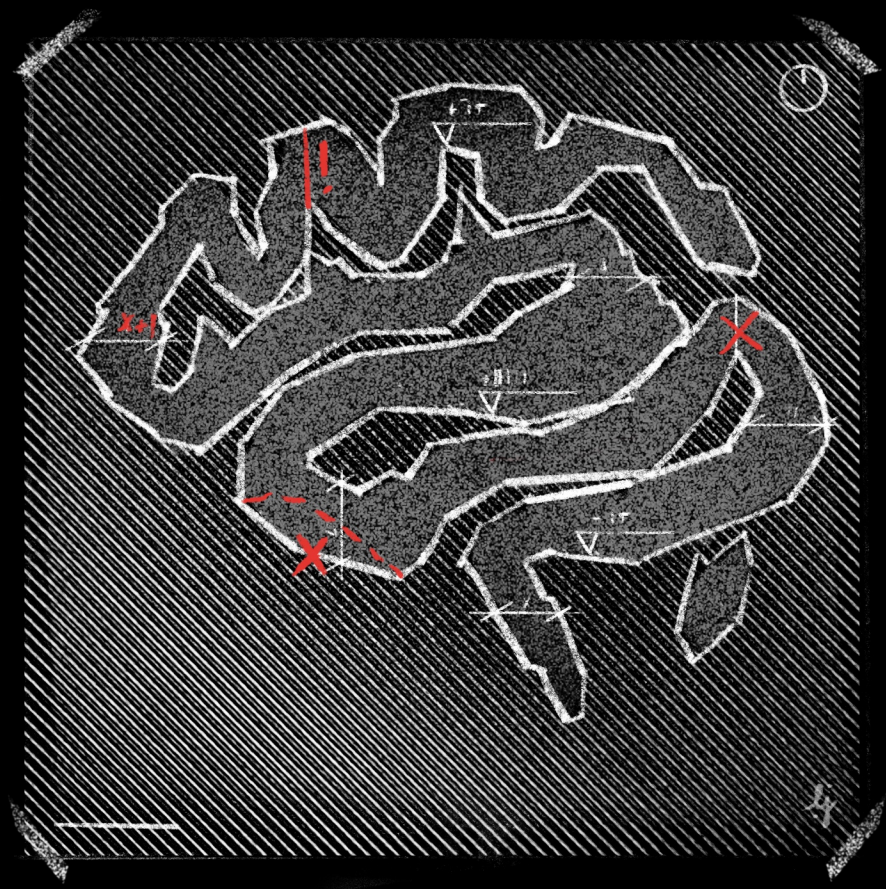
From Chapter 14, The moonshot: population-based studies of aging

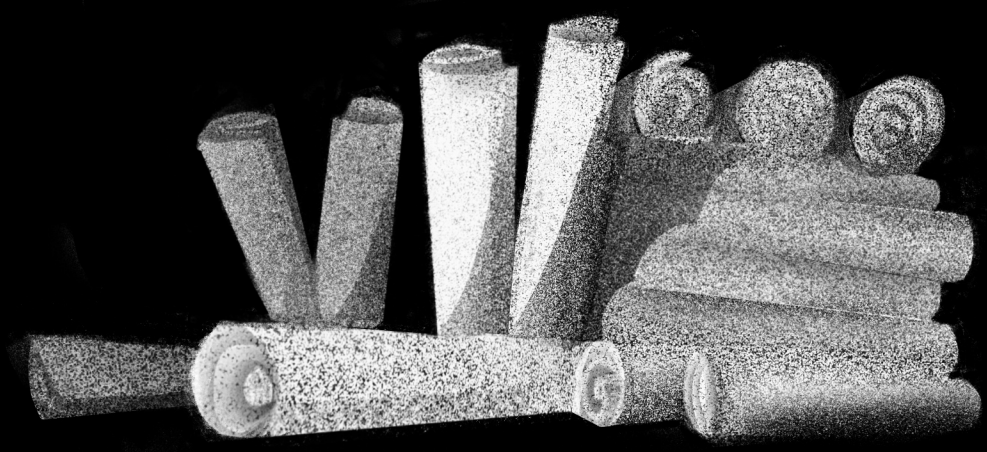
Here is our moonshot. Rather than studying the biological abnormalities of people based on the labels they receive at the bedside, we should study aging itself. The “gold standard” will be the biologic signals, not the symptoms. From very large cohorts, we could identify small groups biologically suitable for therapies we may already have available. This is known as repurposing, matching therapies with those most likely to benefit.











From Chapter 15, Predictions for the 2020s and Beyond

Parkinson's disease is not one puzzle but many. So is Alzheimer's. The century-old protein-based definitions of neurodegenerative diseases will need to give way to biology-based classifications for diseases to be cured one small biological subtype at a time. No models that aim at capturing a complex disease can be relevant for an individual with that disease. A complete reconfiguration of the warfare against Parkinson's and Alzheimer's has begun.