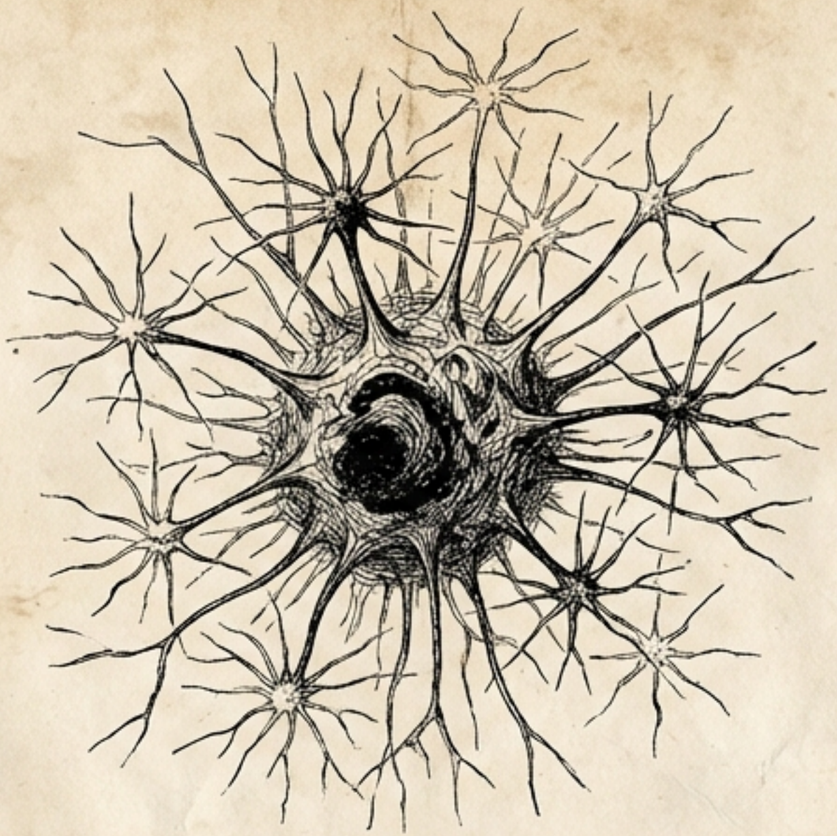

What if the key to solving Alzheimer’s was discovered in 1907, but we’ve spent a century misunderstanding the clues?

Prepared for Dr. James Truchard and Benjamin Gustafsson
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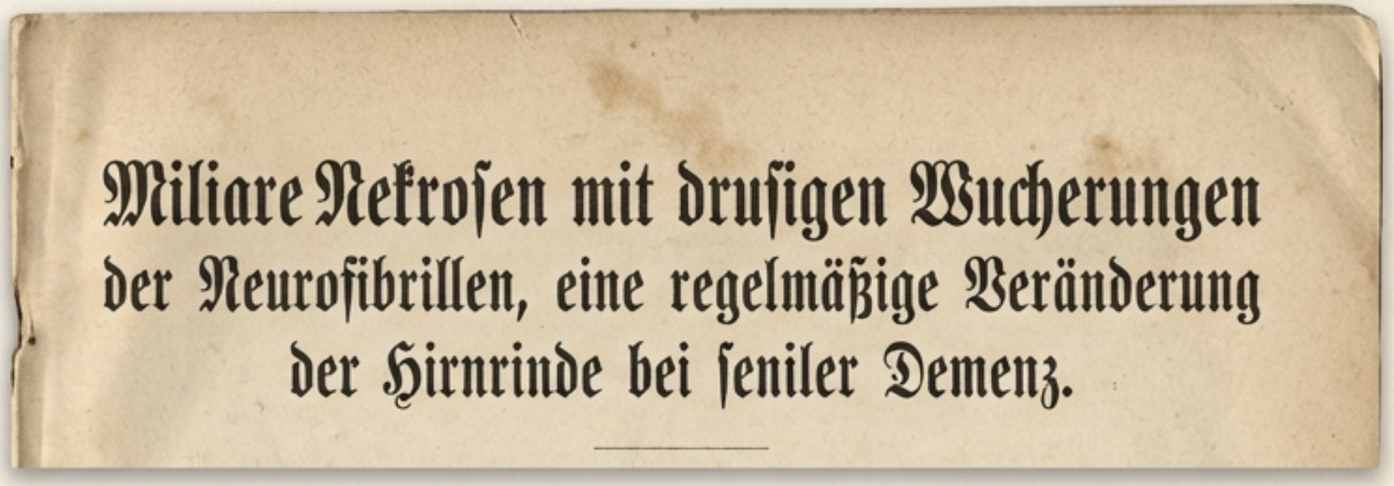
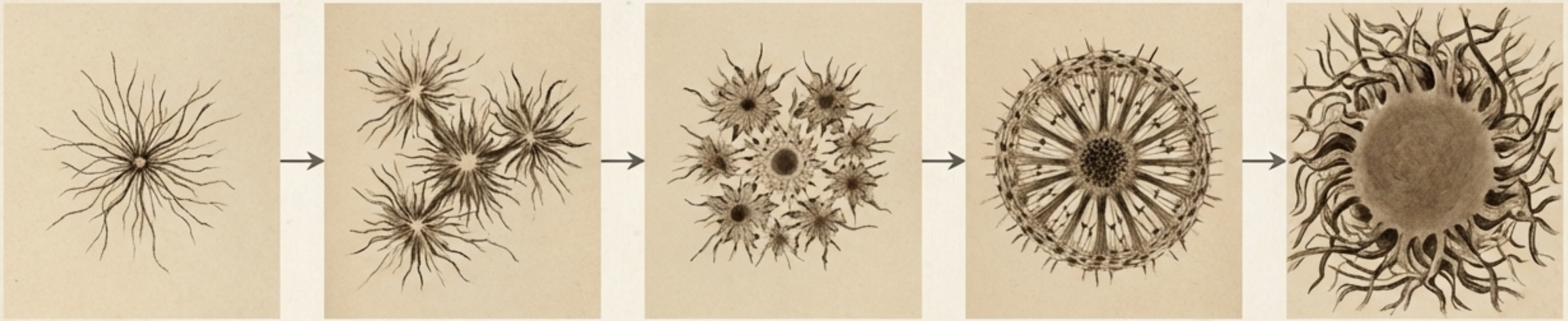
Prague, 1907: The First Investigation



- Oskar Fischer: A systematic clinicopathological study of senile dementia.
- 16 dementia cases examined, establishing a clear correlation between lesions and cognitive decline.
- He documented what he termed “miliary necroses”: the lesions we now call senile plaques.

An Atlas of Neuronal Collapse

Fischer described a progression, a ‘continuum covering early to late clinical phases.’



Stage I: “Little star” formation of fibrils

Stage II: “Morning star” fused clusters

Stage III: Developing a central core

Stage IV: “Wheel-like” stage

Stage V: “Large druse” plaque with a dense, homogenous core

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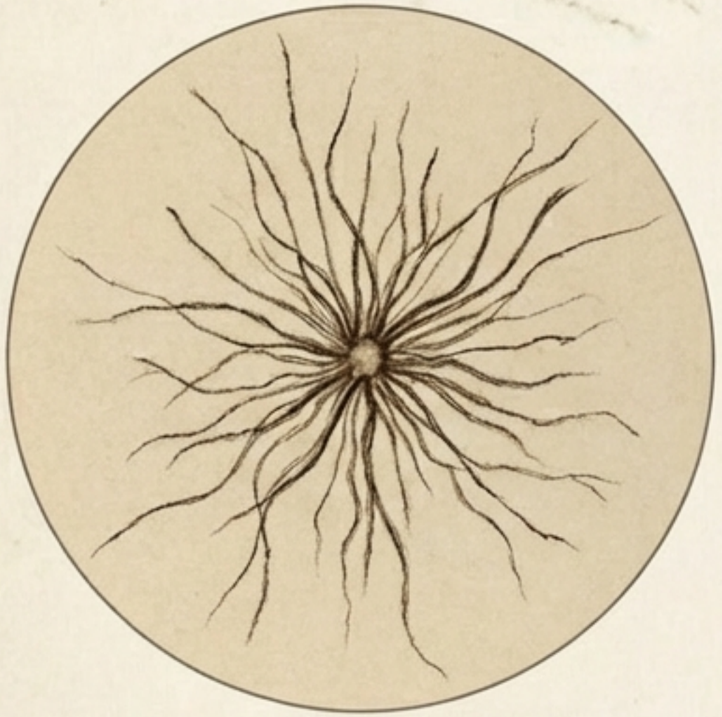
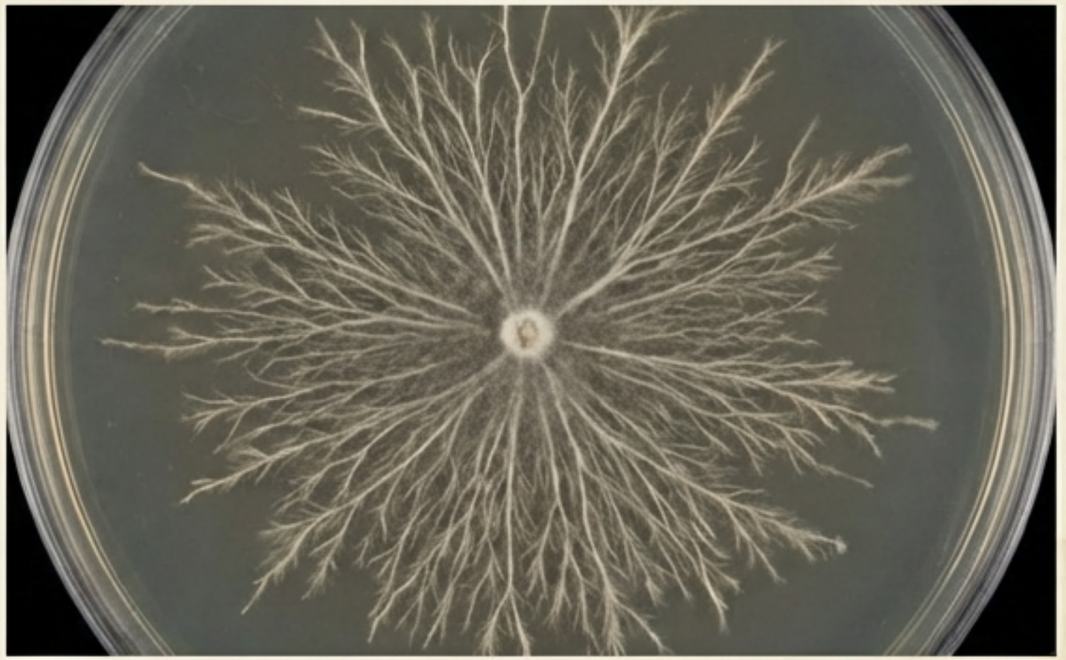
An Infection, or a Degeneration?

Fischer observed that the smallest plaques had a filamentous appearance...





“...reminding one of a bacterial colony.”

He hypothesized a ‘germ’ or chronic infection might trigger the degenerative process he meticulously documented.

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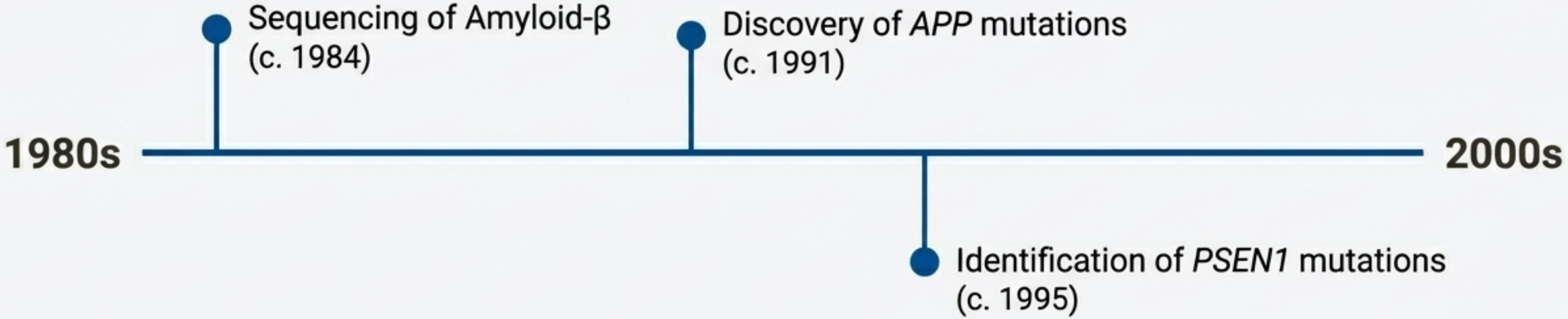
The Investigation Turns to a Prime Suspect: Amyloid



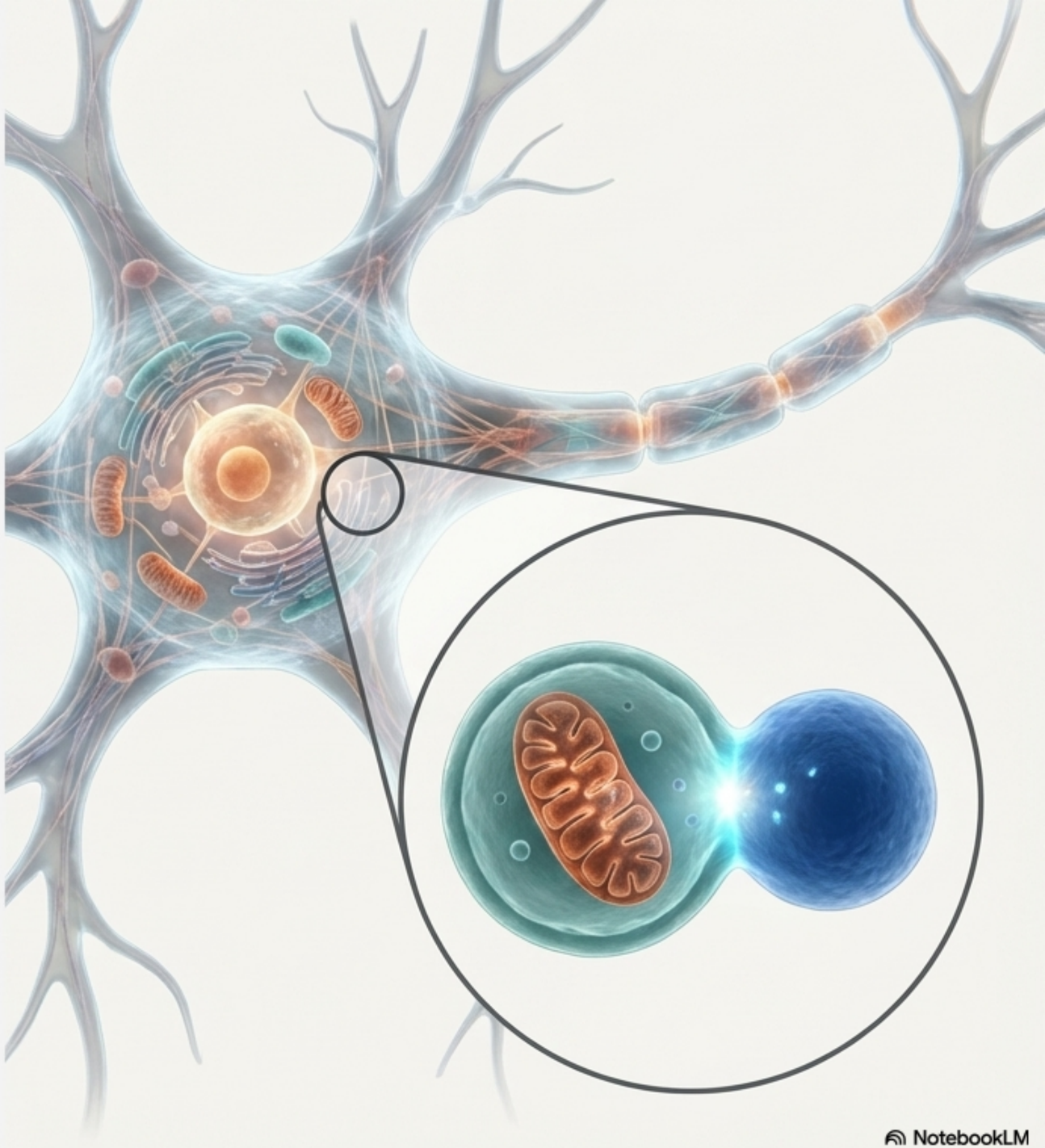
The Dominant Theory: The Amyloid Cascade Hypothesis proposed that the accumulation of Amyloid-β (Aβ) is the primary trigger of neurodegeneration.

The Inconsistency: A critical clue that didn't fit: Amyloid plaque burden does not always correlate with the severity of clinical dementia.

A New Forensic Science Reveals the Crime Scene Within

The Breakthrough: The work of Ralph Nixon and colleagues refocused the investigation from extracellular plaques to the internal machinery of the neuron.

The Process: Autophagy, the cell's essential system for degrading and recycling its own components. In long-lived neurons, this system is critical for survival.



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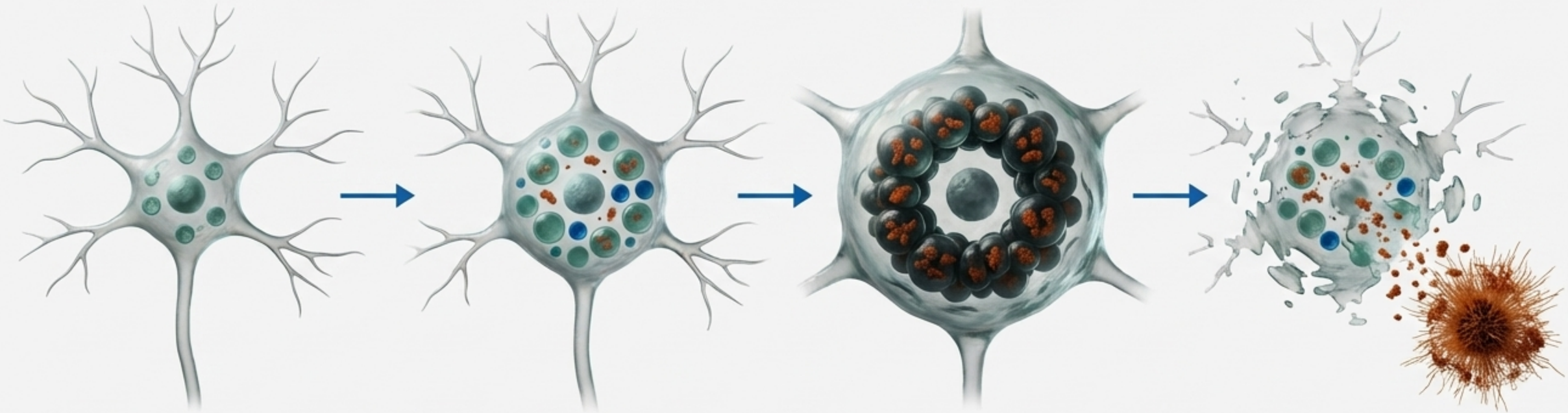
Plaques Don’t Form. They Are Released.

The ‘Inside-Out’ Origin: Evidence shows plaque-like aggregates form *inside* neurons first. The death of these cells, succumbing to autophagic buildup, gives rise to extracellular senile plaques.



1. Induction: A neuron under stress initiates autophagy, forming numerous autophagosomes.

2. Stall: The clearance process stalls. Autophagic vacuoles (AVs) laden with undigested Aβ and other substrates accumulate.

3. Collapse (PANTHOS): The neuron becomes engorged with a ‘poisonous flower' wreath of AVs around the nucleus.

4. Expulsion: The neuron lyses, rupturing and releasing its contents, which coalesce to form an extracellular cored plaque.

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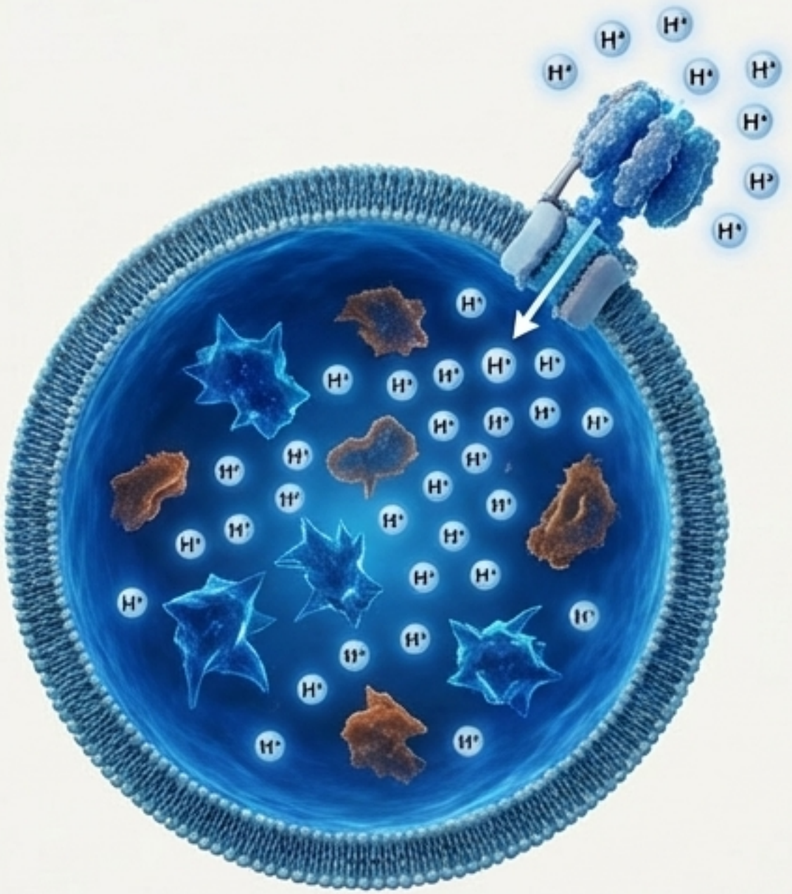
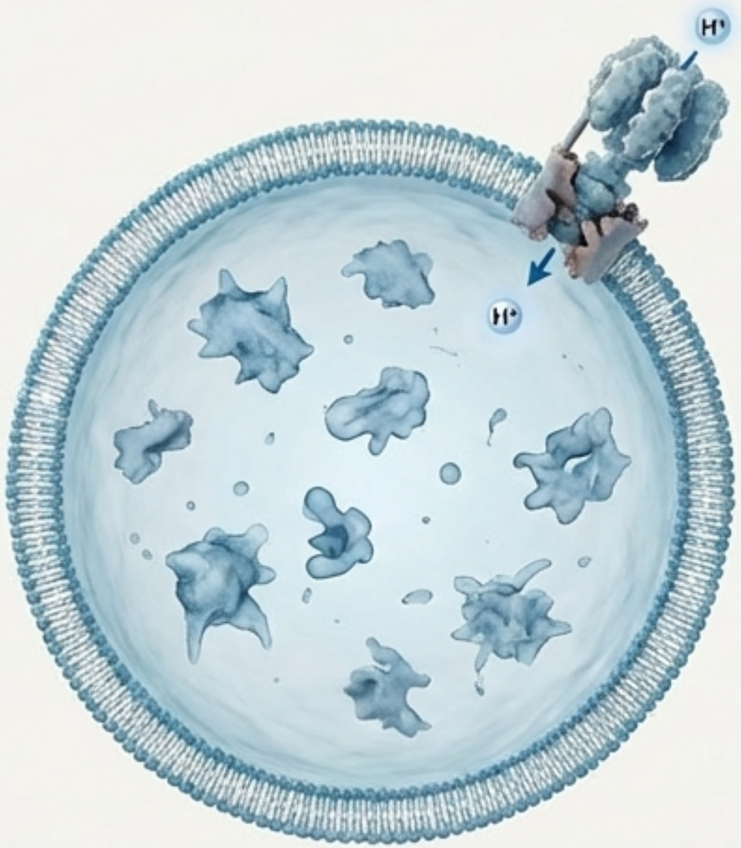
The Smoking Gun: Lysosomal Acidification Failure



Healthy pH ~4.5



Dysfunctional pH ~6.0

The Mechanism: The lysosome's degradative enzymes only function in a highly acidic environment.

The Defect: This acidity is maintained by the v-ATPase proton pump. In Alzheimer's, this pump is compromised, neutralizing the lysosome and halting all effective waste disposal.

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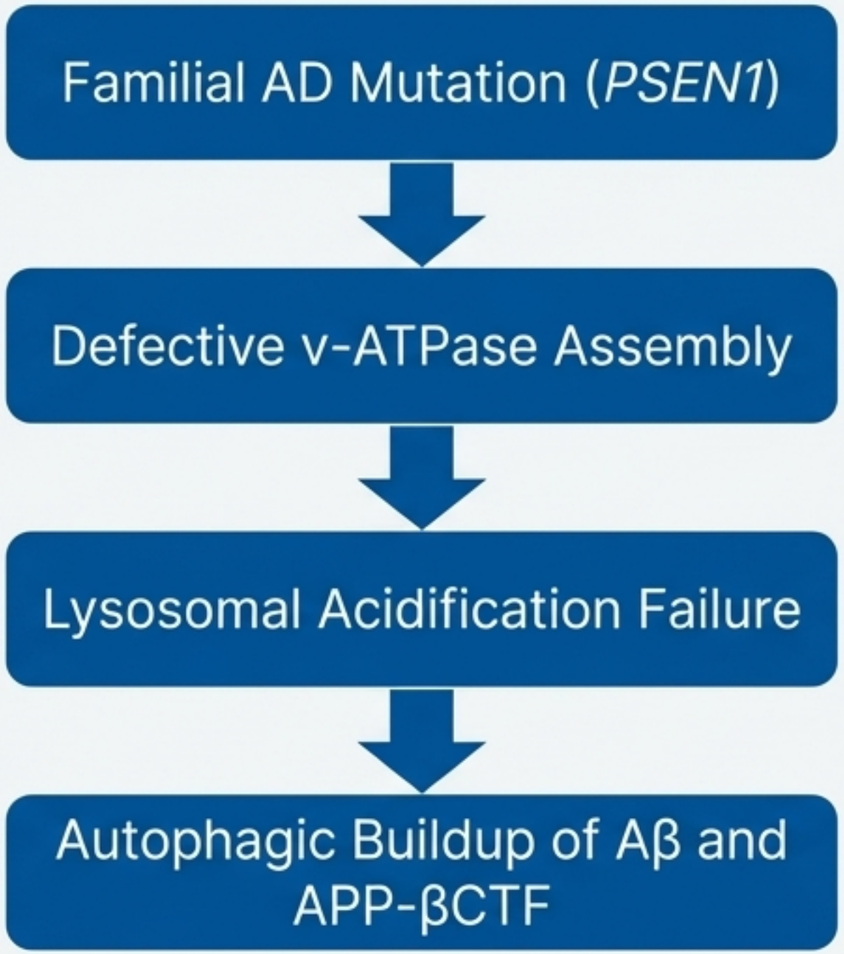
Re-interrogating an Old Suspect



- **The Dual Role of Presenilin-1:** Beyond its role in generating Aβ, *PSEN1* is essential for lysosome acidification.
- **The Finding:** Familial AD mutations in *PSEN1* don't just generate more waste; they cripple the cell's garbage disposal system, creating a catastrophic feedback loop.

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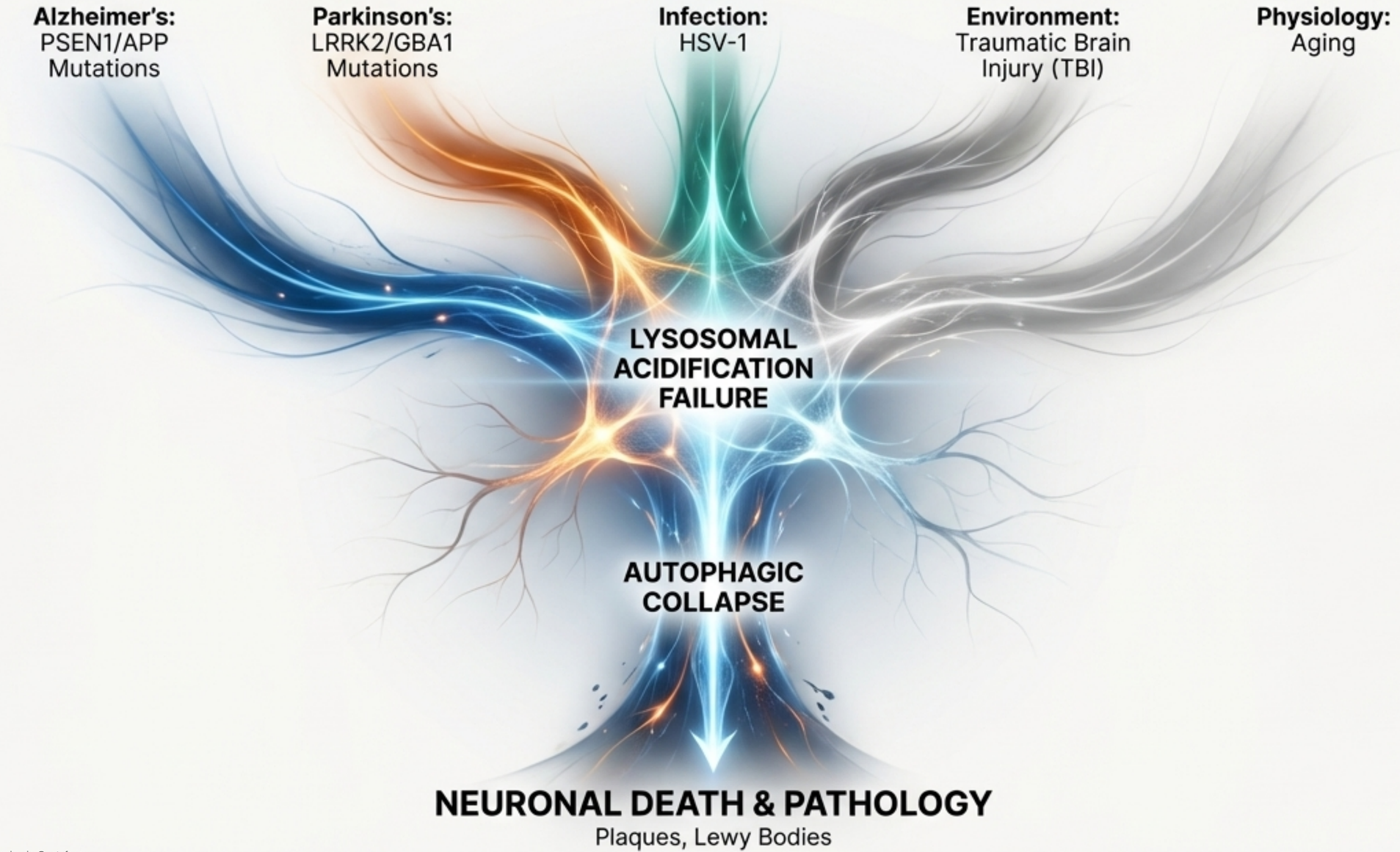
Convergent Autophagic Collapse: A Unified Theory of Neurodegeneration



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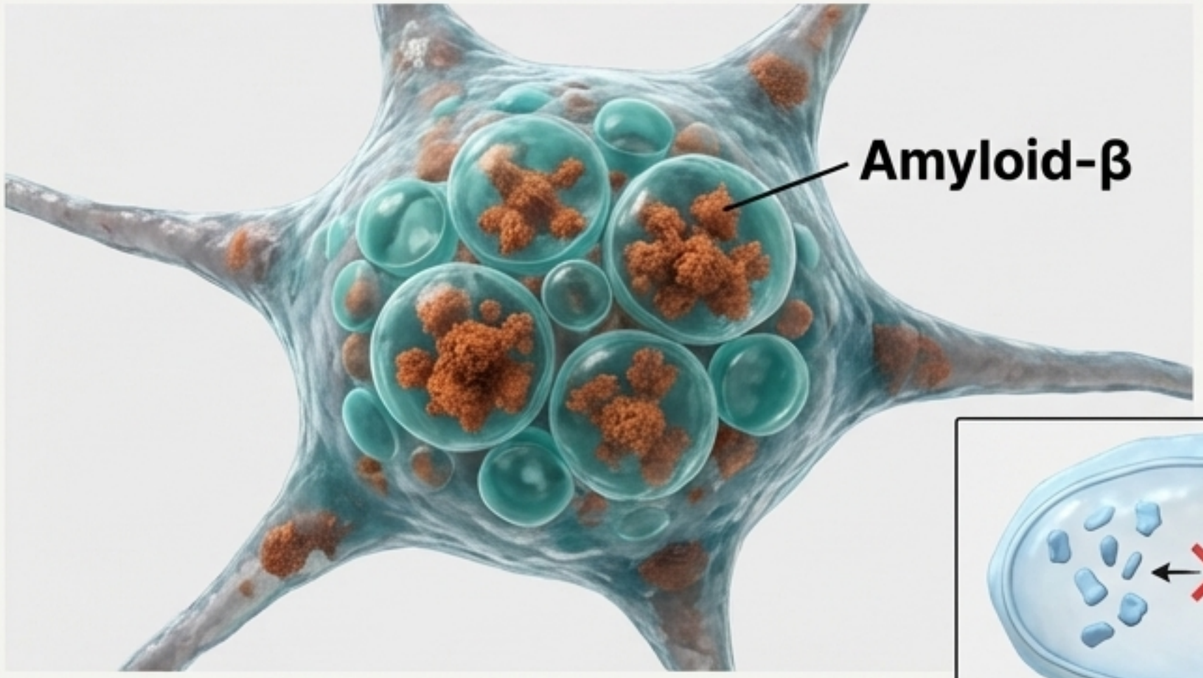
Different Culprits, Same Method

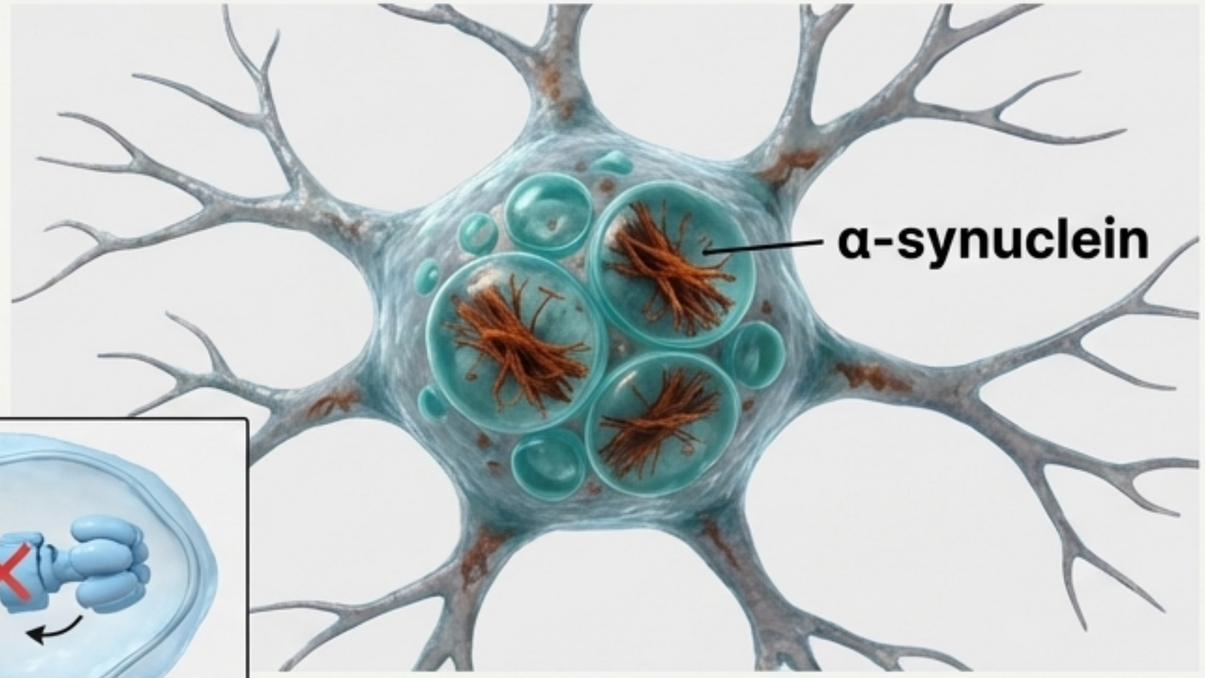
Cellular collapse

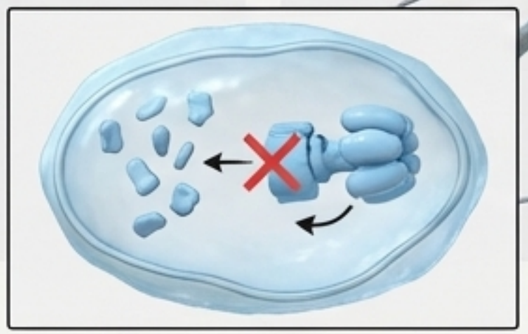
Alzheimer's neuron



Advance collapse

Parkinson's neuron





Dysfunctional Lysosome:
Broken v-ATPase Pump

The Parkinson's Connection

- **_LRRK2_ mutations**: Cause a modest increase in lysosomal pH and reduce autophagic flux.
- **_GBA1_ mutations**: Impair a key lysosomal enzyme, leading to substrate buildup and secondary autophagy failure.

The Principle

The specific protein that aggregates may differ, but the underlying failure of cellular clearance is a shared mechanism.

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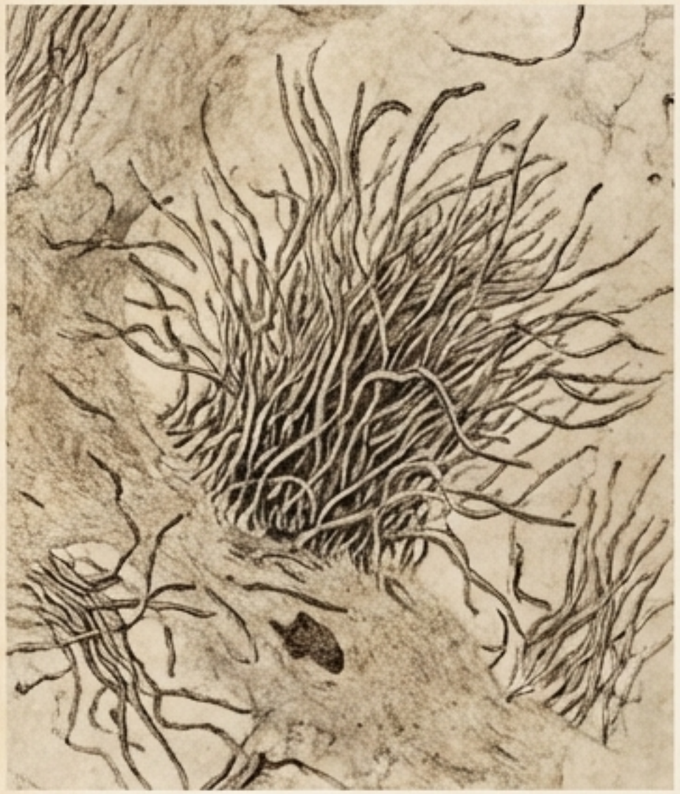
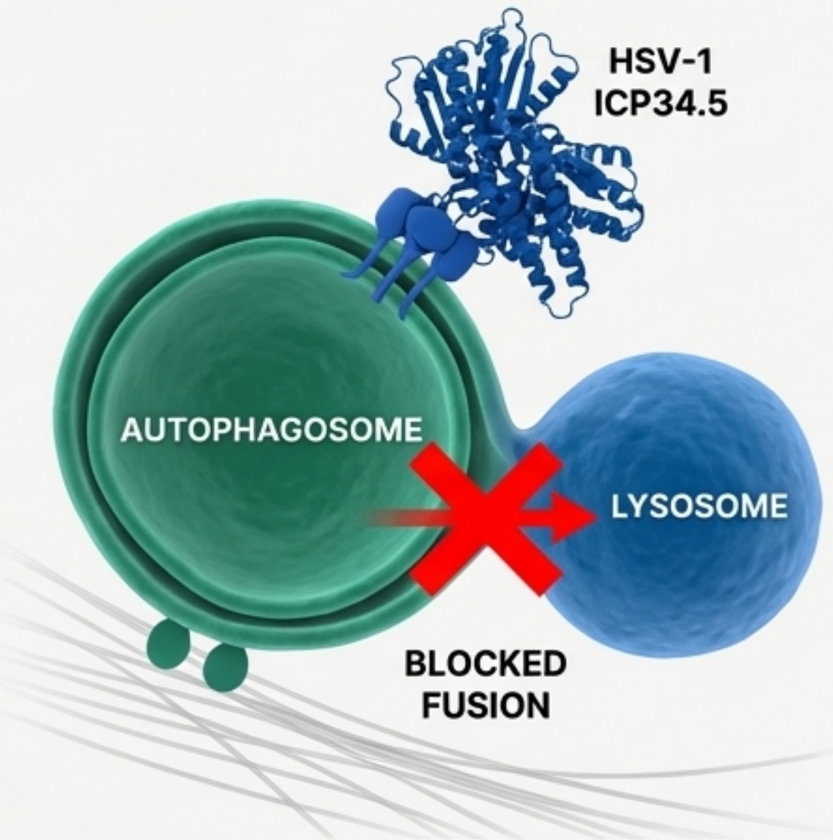
The “Germ” Hypothesis, Revisited



“...reminding one of a bacterial colony.”

A Century-Old Echo: Fischer's speculation of an infectious trigger finds a modern molecular basis.

The Mechanism: Pathogens like *HSV-1* can sabotage the autophagy pathway to evade destruction, creating the exact conditions for autophagic collapse and the accumulation of Aβ. Fischer's "colony" was not the plaque itself, but the trigger for the internal collapse that creates it.



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A New Therapeutic Manifesto

The Old Goal:

~~Clear extracellular protein aggregates.~~

The New Goal:

Restore the neuron’s fundamental proteostatic health.

The Imperative: We must shift focus from treating the pathology to preventing the collapse.

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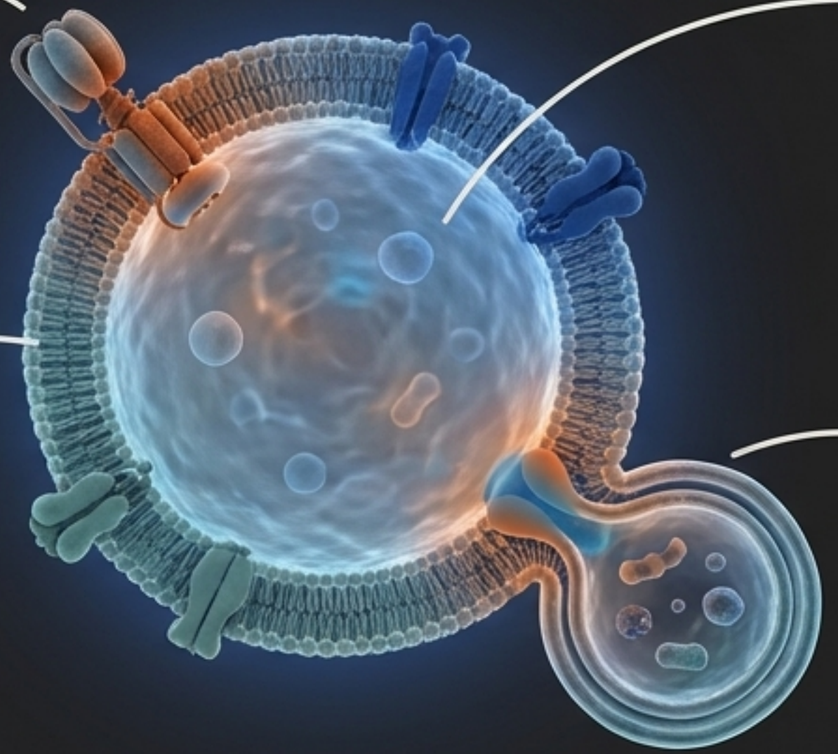
The Arsenal for Restoration

Novel Therapeutic Targets: The Convergent Autophagic Collapse model points to new strategies for intervention:

Enhance Acidification:
Modulators of the v-ATPase proton pump.

Boost Biogenesis:
Activators of TFEB, the master regulator of lysosome production.



Improve Stability:
Compounds that prevent Lysosomal Membrane Permeabilization (LMP).

Increase Throughput:
Drugs that enhance overall autophagic flux.

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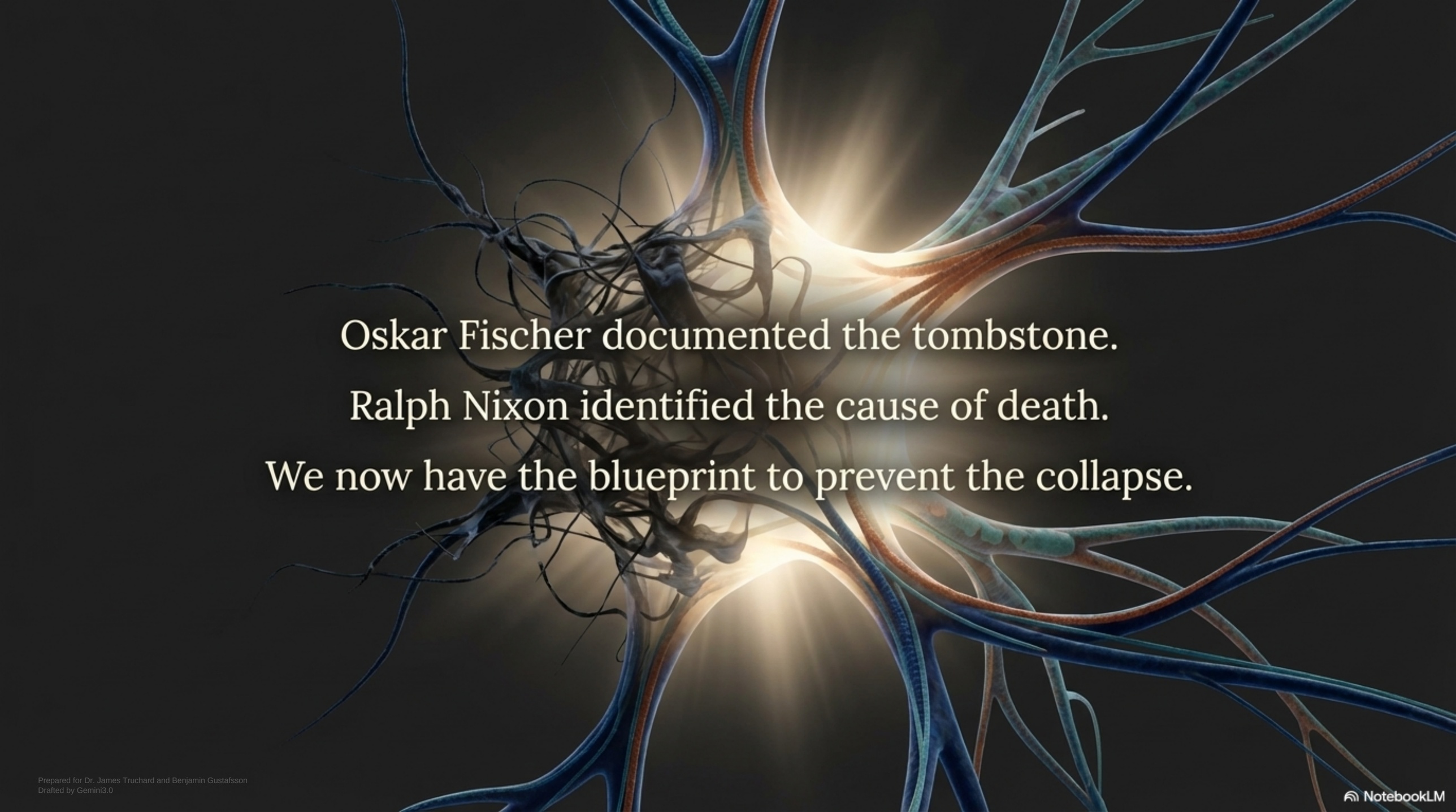

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