nuclein can only “go up” at the expense of the monomeric precursor, which goes down.2

We propose a simple alternative hypothesis: because proteins can only function when normal, the loss of normal, monomeric α-synuclein, as it phase transforms into an insoluble cross-β state known as Lewy pathology, is consequential.3 This idea is testable and falsifiable. If increasing the levels of monomeric α-synuclein to within their normal range proves futile, the proteinopenia hypothesis can be rejected. But where is the falsifiability threshold for the proteinopathy hypothesis? Any hypothesis should be amenable to confirmation or refutation after clinical trials. Unfortunately, our field is known for using clinical trials not to test hypotheses but “to learn.” When trial results do not follow the hypothesis, the lessons usually are that we need better trials and earlier interventions, not better hypotheses.

Bronstein and colleagues remind us that after 2 decades and 42 antiamyloid trials, the field of Alzheimer disease has finally demonstrated slowing of cognitive decline, however marginally, with lecanemab.4 What makes it exceptional among 16 antiamyloid treatments that significantly lowered brain amyloid? Lecanemab markedly increased the levels of CSF amyloid-β 42. One would not know this unless checking figure 5 of the supplementary material. That an antiamyloid therapy might work by elevating CSF amyloid-β 42 is incongruent with a treatment inspired by the assumed toxicity of proteins. Even if we could navigate the paradox of administering an antiamyloid infusion to increase soluble amyloid-β levels, the end would not justify the means. Amyloid clearance results in brain swelling or bleeding in 1 of 4 patients treated with lecanemab and, like most other antiamyloid treatments, accelerates brain atrophy.5

Shortly after the release of our Viewpoint,1 data from 1647 autopsied individuals showed that up to 7 different pathologies can occur in 161 combinations.6 Shockingly, the match between pathology and diagnosis ranged from just 19% to 45%. This study further questions the wisdom of an antiproteinopathy framework to treating neurodegenerative disorders. Rather than seeing proteins as the source of disease, we must recognize them as the victims of many disease processes.

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CORRECTION

Error in Abstract: The Original Investigation titled “Mitigating the Associations of Kidney Dysfunction With Blood Biomarkers of Alzheimer Disease by Using Phosphorylated Tau to Total Tau Ratios,” published May 8, 2023, was corrected to change “higher eGFR” to “lower eGFR” in the second sentence of the Results section of the abstract.


Error in Figure 3: In the Original Investigation titled “Positron Emission Tomography Imaging With [18F]Flortaucipir and Postmortem Assessment of Alzheimer Disease Neuropathologic Changes,” which was published online April 27, 2020, the wrong image was published for Figure 3. The article was corrected online.


Error in Figure 2: In the Original Investigation titled “Effectiveness of Lumbar Cerebrospinal Fluid Drain Among Patients With Aneurysmal Subarachnoid Hemorrhage: A Randomized Clinical Trial,” published online June 18, 2023, there was an error in the lumbar drain group in Figure 2. The value was updated from 24 to 9 for the group with a modified Rankin Scale score of 5 at 6 months. This article was corrected online.