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EDITORIALS

Amyloid-Beta Solubility in the Treatment of Alzheimer's Disease

M. Paul Murphy, Ph.D.

There is general agreement that Alzheimer's disease will become a crisis by the middle of the century. The Alzheimer's Association estimates that 5 million Americans currently have Alzheimer's disease and that their loved ones devote nearly 18 billion hours annually toward their care. If Alzheimer's disease remains unchecked, these numbers are projected to more than triple by 2050, and the economic burden will exceed $1 trillion per year. The quest to find an effective therapy has been urgent. For nearly two decades, since the first report of a successful amyloid-beta (Aβ) immunotherapy in mice,[1] this goal has seemed tantalizingly close.

In this issue of the *Journal*, Honig et al.[2] report the results of the EXPEDITION3 trial of solanezumab, a humanized monoclonal antibody that has been designed to clear soluble Aβ from the brain. This trial was a follow-up to two earlier trials of solanezumab,[3] in which secondary analyses showed a modest effect in slowing cognitive decline. Unfortunately, the EXPEDITION3 trial did not replicate this earlier finding and instead becomes another disappointment for amyloid immunotherapy. Although several trials of other immunotherapies are ongoing, this outcome raises several broader issues.

The EXPEDITION3 trial included only patients with mild cases of Alzheimer's disease who had some evidence of amyloid disease, as determined either by means of florbetapir (an ^{18}fluorine-labeled reagent that binds to Aβ) positron-emission tomography or by means of cerebrospinal fluid measurements of Aβ1-42. Although this effort does not differ substantially from others that have sought to intervene at an early stage of disease, which might be more amenable to treatment, it brings up the question, "How early is early enough?" Researchers have known for some time that the mouse models that we rely on to provide preclinical data are much closer to humans with prodromal Alzheimer's disease than to persons who have the earliest symptomatic stages of the disease.[4] A reasonable argument has been made that antiamyloid therapies may yet work as a primary preventive strategy.[5] For example, persons who have a strong family history of Alzheimer's disease or who have a dominantly inherited amyloid mutation are motivated participants in clinical trials for the prevention of Alzheimer's disease. Although two ongoing trials — DIAN-TU (Dominantly Inherited Alzheimer Network Trial, involving persons with dominantly inherited mutations; ClinicalTrials.gov number, NCT01760005) and A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's Trial, involving persons at risk for Alzheimer's disease; NCT02008357) — will partially address the question of amyloid removal in disease prevention, we are still several years from knowing their results.

The trial conducted by Honig et al. could point to an alternative possibility, one that is potentially more promising (or at least intriguing). The authors point out that solanezumab was highly effective at targeting soluble Aβ. Although it is possible that the magnitude of reduction in soluble Aβ was simply insufficient to create a measurable clinical benefit, recent results from an early trial of aducanumab could indicate that the ability of an antiamyloid therapy to clear insoluble Aβ is an important factor in

the success of treatment.[6] If clearing previously deposited amyloid from the brain is more important than preventing its production, this could also at least partially explain the lack of success with other strategies such as beta-secretase inhibitors that have, after initial promise,[7] proved disappointing.[8] It is also possible that some other characteristic of aducanumab, such as its relatively higher penetration in the brain, as compared with solanezumab, explains the difference. A final determination rests on the outcome of ongoing studies of aducanumab (ENGAGE [NCT02477800] and EMERGE [NCT02484547]), which expand the scope to an international trial (at different sites).

Although it may not quite be time to give up on Aβ immunotherapy for treating Alzheimer's disease, it would be foolish to ignore the continued failures of antiamyloid approaches. In spite of the mountain of evidence supporting the primacy of Aβ in Alzheimer's disease, many researchers are coming to the realization that our preclinical models of the disease may be missing the mark. Even if there is some future success in a primary prevention trial, there is still little headway being made in improving the treatment of Alzheimer's disease. There is some hope that a combination of therapeutic approaches might help, since there is evidence that the different pathologic aspects of Alzheimer's disease are interactive.[9] Whether a multifaceted strategy or something entirely unforeseen is the answer, the field is clearly in need of innovative ideas. We may very well be nearing the end of the amyloid-hypothesis rope, at which point one or two more failures will cause us to loosen our grip and let go.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Progress in the Treatment of Hodgkin's Lymphoma

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Although there has been considerable research activity in the treatment of Hodgkin's lymphoma since advanced stages of the disease became curable with combination chemotherapy in the 1960s, the most significant advances have involved the maintenance of a particular level of antitumor efficacy while acute and late toxic side effects and their attendant mortality are reduced. These advances include the preservation of high response rates at reduced levels of toxicity with the current standard regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); the demonstration that various forms of radiation therapy were associated with unacceptably high levels of long-term toxicity; the application of high-dose salvage chemotherapy; and the tailoring of treatment to the evidence of response revealed on midterm positron-emission tomography (PET). Little progress has been made in improving overall survival.

Two notable exceptions to this general lack of progress in the development of newer approaches to treatment are the application of the CD30 immunotoxin brentuximab vedotin[1] and the programmed death 1–inhibitor nivolumab[2] to the treatment of patients with Hodgkin's lymphoma