On this issue of the Archives, Lo et al describe longitudinal changes in cerebrospinal fluid (CSF) β-amyloid 42 (Aβ42), fludeoxyglucose–positron emission tomography, and magnetic resonance imaging hippocampal volume and associated cognitive loss in normal aging, mild cognitive impairment (MCI), and Alzheimer disease (AD). The trajectories of these biomarkers, they find, vary across different cognitive stages. Their findings show that CSF Aβ42 declines prior to the beginning of cognitive loss. Glucose metabolism measuring neuronal dysfunction falls next, followed by neuronal injury and loss as defined by hippocampal atrophy. Their data provide compelling evidence that amyloid deposition occurs early in the disease process, before hypometabolism or hippocampal atrophy, “suggesting that biomarker prediction for cognitive change is stage dependent.” Their study is in agreement with that of Jack et al, expressing the view that Aβ42 deposition leading to formation of Aβ plaques occurs while individuals are still cognitively normal, leading after a lag period to neuronal dysfunction, metabolic impairment, and neurodegeneration with neuronal loss and brain atrophy.

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Holmes et al reported the neuropathological findings of individuals with AD who had been immunized with full-length Aβ42 and had entered a phase-1, randomized, placebo-controlled trial of immunization with Aβ42 (AN1792, Elan Pharmaceuticals) in September 2000. They showed that immunization of patients was associated with long-term reduction in Aβ42 load compared with unimmunized controls subjects. Despite the reduced brain Aβ42 levels in these patients and even dramatic reductions in two, all immunized recipients continued to progress with cognitive loss and all developed severe and unremitting dementia. The causes of the continued, unrelenting dementia process, despite significant reductions in brain Aβ42 load levels, are not clear, but it can be argued that early deposition of Aβ42 in plaques and as oligomers invokes secondary downstream pathologies including hyperphosphorylated tau, tangles, cytotoxic cytokines, oxidative stress, and neuronal loss, which, after time, become autonomous and independent of the inciting presence of amyloid.

The data from Lo et al emphasize that a narrow but vital window of opportunity exists for preventing AD but it correlates with the time when patients do not yet have dementia and are not even significantly impaired with serious memory loss. Deposition of Aβ42, in the cascade of the neuropathologies that will cause AD, begins when the individual is still cognitively normal or has early cognitive loss, before altered glucose metabolism, and long before hippocampal atrophy. The amyloid cascade hypothesis, that it is amyloid that initiates first the series of neuropathological changes that produce AD, remains challenged but has not been tested rigorously with a potential therapy given early enough to test its basis, prior to the instigation of other confounding neuropathological changes.

So what do we do and what can be recommended as a way forward? First and foremost is to develop therapy that can be given early in patients with, at most, incipient memory loss, that will delay or arrest the earliest abnormalities when the reparative processes of brain can respond. Antiamyloid therapy based on the data of Lo et al and De Meyer et al clearly will only have a chance of being effective when Aβ42 is minimally accumulating and before secondary neuropathological changes begin.

In “Sharpen That Needle,” Herskovits and Growdon commented on the data of De Meyer et al, stating that identifying a signature low CSF Aβ42 level, high total tau protein level, and elevated phosphorylated tau protein predicted well the conversion of MCI to AD, providing a means of CSF analysis when “implemented as a screening test, can identify clinically healthy individuals at risk for MCI and AD.” So CSF analysis identifying an individual as being at high risk for cognitive loss, and possibly AD, would recommend the individual for a positron emission tomography–amyloid scan; if it shows Aβ42 accumulation, the individual would be a candidate for preventive therapy in general and antiamyloid therapy in particular.

It is incumbent on the AD research community to educate our colleagues, the public, and regulatory agencies to accept that it is necessary to treat AD before it is symptomatic. Alzheimer disease therapies must be allowed to be given in rigorous, phase-1 clinical trials to individuals who have progressive memory loss or mild cognitive impairment, before they are diagnosed with dementia due to AD, when preventive therapy has a chance to succeed.

In our research to develop a DNA anti-Aβ42 vaccine as preventive therapy for AD, we have encountered the idea that it should be clinically tested only after the diagnosis of AD has been made. The lessons from Holmes et al is that it is now necessary to move the clock backward as early as possible, when the patient has the optimal opportunity to respond to the therapy. There are...
now many therapeutic compounds being developed for AD. Lo et al,1 De Meyer et al,9 Herskovits and Growdon,10 and my belief and experience say that therapeutic progress will depend on biomarker detection of risk of AD, with prompt initiation of safe preventive therapies before the patient is diagnosed with the disease.

Roger N. Rosenberg, MD

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Author Affiliation: Department of Neurology, University of Texas Southwestern Medical Center, Dallas.

Correspondence: Dr Rosenberg, Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9036 (roger.rosenberg@utsouthwestern.edu).

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