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Lifelong Management of Amyloid-Beta Metabolism to Prevent Alzheimer's Disease

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Twenty-five years ago, the cloning and localization to chromosome 21 of the Alzheimer's amyloid-beta ($A\beta$) precursor protein (APP)¹ made clear that the early-onset form of Alzheimer's disease that occurs in all patients with Down's syndrome² is apparently attributable to an extra copy of *APP*. Proamyloidogenic *APP* missense mutations were subsequently identified in families with autosomal dominant Alzheimer's disease,³ and a substantial proportion of cases of autosomal dominant Alzheimer's disease have been linked to more than 200 proamyloidogenic mutations in the catalytic subunits of γ -secretase (known as presenilin 1⁴ and 2⁵) that are responsible for the liberation of $A\beta$ from APP.

By 1999, $A\beta$ -depositing transgenic mice had been vaccinated with $A\beta$ and were found to form anti- $A\beta$ antibodies that could prevent cerebral amyloidosis.⁶ The first clinical success in humans was reported in 2003 in a postmortem study showing that vaccinated participants had extraordinarily sparse levels of cortical amyloid plaques.⁷ In 2010, passive immunotherapy with a monoclonal anti- $A\beta$ antibody was shown to retard the progression of the carbon 11-labeled Pittsburgh compound B (PIB)-positive fibrillar cerebral amyloid burden by 15 to 25%.⁸ However, this modest reduction in plaque burden was associated with no obvious clinical benefit or arrest in the progression of cognitive decline. A larger study with the same monoclonal anti- $A\beta$ antibody but with more power for detecting treatment effects confirmed the absence of clinical benefit.⁹

The absence of cognitive benefit may have been because the modest reduction of PIB-positive fibrillar amyloid was insufficient to effect substantial retardation of neurodegeneration or because anti- $A\beta$ monoclonal antibody treatment was too late. There is growing interest in $A\beta$ -lowering therapies for presymptomatic disease.^{10,11} In this issue of the *Journal*, Bateman et al.¹² report findings from a study focusing on imaging and biomarker assessments in presymptomatic autosomal dominant Alzheimer's disease, called the Dominantly Inherited Alzheimer Network (DIAN) study.

In collaboration with the DIAN investigators, Bateman and colleagues identified, clinically characterized, and followed (by means of imaging and measurement of body-fluid biomarkers) many of the families with autosomal dominant Alzheimer's disease worldwide. Important for the prevention trials ahead, existing knowledge had already established that, within a particular kindred and its own mutation, the age at onset breeds true — that is, age

at onset is relatively invariable from generation to generation. Therefore, each mutation carrier knows approximately how many more presymptomatic years he or she can expect. The DIAN study showed that the changes in levels of $A\beta_{42}$ in the cerebrospinal fluid (CSF) that accompany $A\beta$ deposition can be detected as long as 25 years before a particular person's symptoms begin. This implies that primary prevention in persons with mutations for autosomal dominant Alzheimer's disease might need to begin 25 years or more before expected symptom onset. The "\$200 billion question" (the cost of Alzheimer's care in the United States this year) is: How early must one intervene in order to perpetually delay the onset of symptoms (i.e., until the end of life) in all persons?

Jonsson et al.¹³ recently announced the discovery in Iceland of a rare mutation that inhibits β -secretase cleavage of APP, leading to extremely low levels of plasma $A\beta$ and of $A\beta$ in the CSF and to protection against Alzheimer's disease. One of the extraordinary features of this study was the identification of 25 persons homozygous for *APOE $\epsilon 4$* who were apparently protected from Alzheimer's disease by the APP mutation. These data solidify the notion that cerebral $A\beta$ accumulation is required for Alzheimer's disease pathogenesis and also point to β -secretase inhibition as an especially attractive and potentially effective target. These data provide one answer to the \$200 billion question: lifelong reduction of $A\beta$ levels by approximately 50% is apparently sufficient to prevent Alzheimer's disease while producing no obvious deleterious effects.

Until the DIAN data appeared, most Alzheimer's disease researchers estimated that $A\beta$ accumulation in the brain began 10 to 15 years before symptoms. We now know that, at least for autosomal dominant Alzheimer's disease, the onset — or at least the initiation of aberrant APP metabolism that leads to $A\beta$ accumulation — is likely to be a decade earlier than we had guessed. Although the DIAN data indicate that the CSF changes predate the amyloid imaging changes, initiation of anti- $A\beta$ therapy at the first sign of $A\beta$ accumulation may already be too late to guarantee avoidance of dementia for the remainder of the natural life span.

What do the DIAN data portend for patients with Down's syndrome?² Should they be started on $A\beta$ -lowering therapy as babies? As children? As adolescents? The knowledge that the pathologic features of Alzheimer's disease develop in all patients with Down's syndrome by 45 years of age² suggests that clinical trials of $A\beta$ -lowering therapies in that population should begin no later than 20 years of age. By using a strategy analogous to that underlying the DIAN study, longitudinal studies of amyloid imaging in this vulnerable population should help narrow down the age at which intervention should be initiated. Are there other at-risk populations that might benefit from lifelong management of $A\beta$ metabolism, such as carriers of the *APOE $\epsilon 4$* allele; boxers; football, soccer, and hockey players; or military recruits anticipating battlefield exposure?^{14,15}

Should we begin to think of lifelong control of $A\beta$ metabolism in the same way that we now think of lifelong control of cholesterol metabolism? The lesson of the DIAN study¹² and of the study on the protective APP mutation¹³ is that reduction of the risk of late-life dementia requires a long-term and possibly lifelong effort. What is also clear — regardless of whether, in light of the protective APP mutation, one considers the "amyloid hypothesis of

Alzheimer's disease" as proven or not — is that any comprehensive strategy aimed at reduction of late-life dementia risk will almost certainly include monitoring and immunopharmacologic or neuropharmacologic control of A β metabolism.

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