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Late-Life Dementias: Does This Unyielding Global Challenge Require a Broader View?

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Late-life dementias, especially Alzheimer disease, have profound effects on aging individuals. Demographic trends suggest that without interventions to effectively prevent or treat Alzheimer disease and related dementias, societies that enjoy the benefits of longevity could be overwhelmed and dramatically changed by the challenges and burdens of large numbers of cognitively impaired older persons. According to a recent review, “If the pace of increase in life expectancy in developed countries over the past two centuries continues through the 21st century, most babies born since 2000 in France, Germany, Italy, the UK, the USA, Canada, Japan, and other countries with long life expectancies will celebrate their 100th birthdays.”¹ In general, prevalence rates for dementia are estimated to double every 5 years after age 65. Rates of dementia in community studies increase from 30% for persons aged 85 through 89 years to 50% for persons aged 90 through 94 years to 74% for those 95 years or older.² Given the burden of dementia on patients, families, and caregivers, the high rates in late life, and the clear demographic trends, it is imperative for research to find solutions that prevent, delay, slow, and treat Alzheimer disease and related dementias. It would be difficult to overstate the urgency of this need.

Two studies^{3–4} in this issue of *JAMA* illustrate complementary approaches in clinical research. In seeking to alter the course of disease, most experimental therapeutics have been based on the “amyloid beta (A β) hypothesis” that proposes excess accumulation of A β peptides as the common etiology for Alzheimer disease, with a derivative complex series of steps that includes accumulation of abnormally phosphorylated tau protein. Therefore, a major goal has been suppression of the sequentially catalyzed endoproteolytic cleavage of a normally expressed protein called amyloid precursor protein (APP) by β -site APP cleaving enzyme (BACE) and γ -secretase to yield A β peptides.⁵

The report by Green et al³ presents results from the first trial of a γ -secretase modulator for the treatment of Alzheimer disease. The goal of this class of drug is to alter γ -secretase activity to favor production of shorter, less neurotoxic forms of A β peptides rather than simply inhibiting γ -secretase activity, which appears to carry toxicity, especially from suppression of the Notch signaling pathway.⁶ The study by Green et al was restricted to patients with mild Alzheimer disease and represents the largest treatment trial for the condition to date. With 18 months of follow-up, it was adequately powered and designed to detect delayed progression of disease. The important conclusion from their null findings is that stated by the authors: “Our

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results are also a reminder that interventions affecting amyloid [beta] have not yet been shown to alter the course of AD.”³

This is yet another example among several drug candidates with demonstrated efficacy in transgenic mouse models of overproduction of cerebral A β peptides that failed to translate into demonstrated benefit for patients. There are many potential reasons for these failures. One is that the treatment did not achieve the expected pharmacologic effect of shifting A β peptide cleavage toward shorter peptides; there are no data on this critical point, just expectations based on experiments in mice. Another often promoted explanation is that intervention is more likely to be effective at the earliest stages of disease, ideally preclinical. Success in this case requires developing biomarkers and disease surrogates that can be incorporated into prevention trials. In addition, commonly used experimental models of Alzheimer disease may inadequately reflect the complexity of cognitive impairment and dementia in older patients and thereby provide falsely promising leads.

Worldwide, population-based studies with brain autopsy end points have repeatedly demonstrated that dementia is a convergent phenotype derived from the confluence of at least 3 common disease processes: Alzheimer disease, vascular brain injury (especially from small vessel disease), and Lewy body disease. These diseases variably combine in each patient to produce the dementia syndrome.⁷ Thus, a “comorbidity problem” confounds studies that rely on clinical criteria that are excellent at detecting Alzheimer disease but do not adequately discern actual or concomitant vascular brain injury or Lewy body disease as the cause of dementia. The convergence of common disease processes, while challenging to traditional research, offers multiple opportunities to develop treatment and prevention strategies. Indeed, the history of successful prevention of another complex disease of aging—atherosclerosis—and the attendant reduction in the burden of myocardial infarction and stroke demonstrate that interventions need not focus on a single pathophysiologic process but rather target multiple processes that affect or influence disease progression.

Observational and community-based studies and early trials suggest that the most readily modifiable risk factors for dementia are those associated with vascular disease. The study by Lieb et al,⁴ also in this issue of *JAMA*, presents intriguing results from the Framingham cohort: higher levels of plasma leptin were associated with reduced risk of Alzheimer disease. These results could be important for several reasons. Leading biomarker candidates have focused on the means of detecting abnormal metabolism of A β peptides by positron emission tomographic imaging or quantification of a particular A β peptide and tau in cerebrospinal fluid; however, it is difficult to imagine that these complex or costly research methods can be adapted as routine for the millions of individuals who need clinical care. To date, all searches for peripheral biomarkers for Alzheimer disease have either failed or await validation; Lieb et al⁴ correctly note that validation of plasma leptin concentration as a biomarker is the critical next step. Based on the convergent complexity of Alzheimer disease and other late-life dementias, we are skeptical that a single peripheral biomarker will be sufficiently discerning for primary practice. However, if confirmed, these results would provide a rationale for pursuing questions focusing on peripheral and central nervous system leptin biology in the earliest stages of neurodegeneration.

The apparently strong association of high leptin levels with lower risk of Alzheimer disease could provide additional insight into pathways involved in the complex processes affecting late-life neurodegeneration. Descriptive studies have shown that obesity in midlife is associated with increased Alzheimer disease risk,⁸ whereas in late life, the reverse appears to be true. Similarly, modification of vascular risk by statins and presence of hypertension is more evident in midlife than in late life when dementia commonly manifests.⁹⁻¹⁰ Habitual exercise appears to protect individuals with subjective memory complaints¹¹ from cognitive decline and in

descriptive studies, habitual exercise is associated with significant reduction in risk of Alzheimer disease and all-cause dementias.¹² As presented by Lieb et al, leptin levels have been demonstrated to correlate with Alzheimer disease risk. Lieb et al cite important evidence from animal studies suggesting that leptin may have direct effects on brain function and on A β peptide metabolism. Whether this represents a truly “new pathway” relevant to brain function in late life, independent of established neurodegenerative or vascular risk factors, remains to be seen.

The null outcome for the leading γ -secretase modulator in a phase 3 trial and the surprisingly strong association between plasma leptin and incident Alzheimer disease underscore the need to broaden the current view of potential therapeutic approaches to cognitive impairment and dementia in older individuals. Research must seek a fuller understanding of the complex convergence of Alzheimer disease with vascular disease and Lewy body disease, the application of biomarkers and other surrogates to clinical trials to quantify specific pharmacologic effects, and a multimodal approach to prevention and treatment. Doing so could have profound effects on the increasing numbers of older persons and on the societies confronting the global challenge of late-life dementias in decades to come.

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