

Series Introduction: Alzheimer's disease: perspectives for the new millennium

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Perspective

This Perspectives series on Alzheimer's disease is dedicated to the late Professor Henry M. Wisniewski, whose ceaseless devotion to the field over the last four decades has paved the way for many more decades of discovery and hope in the battle against this dreadful disease. Age-related impairments in cognition and memory have been known since ancient times, but the clinical-pathological features of the syndrome, now termed "Alzheimer's disease" (AD), were not documented in the medical literature until the first decade of this century. It is now established that AD, a complex and genetically heterogeneous disorder, is the most common type of dementia occurring in mid-to-late life, affecting 7–10% of individuals over 65 years of age and perhaps 40% of persons over 80 years of age. The prevalence of this disease, which now affects more than 4 million individuals in the US, is increasing because of very significant shifts in life expectancy and demographic parameters; it is estimated that in 2050, about 25% of the population will be over 65 years of age. In 1907, Alois Alzheimer reported the case of a middle-aged woman who developed memory deficits and progressive loss of cognitive abilities accompanied by morbid jealousy. Autopsy disclosed the now-recognized classic pathology of AD — the presence of numerous neurofibrillary tangles (NFTs) and senile plaques (SPs) in the neocortex [...]

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SERIES
on Alzheimer's disease

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Age-related impairments in cognition and memory have been known since ancient times, but the clinical-pathological features of the syndrome, now termed "Alzheimer's disease" (AD), were not documented in the medical literature until the first decade of this century. It is now established that AD, a complex and genetically heterogeneous disorder, is the most common type of dementia occurring in mid-to-late life, affecting 7–10% of individuals over 65 years of age and perhaps 40% of persons over 80 years of age. The prevalence of this disease, which now affects more than 4 million individuals in the US, is increasing because of very significant shifts in life expectancy and demographic parameters; it is estimated that in 2050, about 25% of the population will be over 65 years of age.

In 1907, Alois Alzheimer reported the case of a middle-aged woman who developed memory deficits and progressive loss of cognitive abilities accompanied by morbid jealousy. Autopsy disclosed the now-recognized classic pathology of AD — the presence of numerous neurofibrillary tangles (NFTs) and senile plaques (SPs) in the neocortex and hippocampus. The majority of patients with the "sporadic AD" disease exhibit clinical signs during the seventh decade, whereas individuals with inherited AD (see below) often become demented in mid-life. Affected individuals show abnormalities of memory, problem solving, language, calculation, visuospatial perceptions, judgment, and behavior; some cases show psychotic symptoms, such as hallucinations and delusions. Activities of daily living become increasingly impaired; in late stages of the disease, patients are often mute, incontinent, and bedridden and usually die of intercurrent medical illnesses.

AD selectively affects neurons in certain brain regions and neural systems, including nerve cells in the cortex, hippocampus, amygdala, anterior thalamus, basal forebrain, and several brainstem monoaminergic nuclei. Many affected nerve cells exhibit intracellular accumulations of NFTs, poorly soluble filaments comprised principally of phosphorylated tau, a microtubule-associated protein. Because phosphorylated tau binds microtubules poorly and alters their stability, modifi-

cations of tau could have effects on intracellular transport, cellular geometry, and neuronal viability. SPs, abundant in the amygdala, hippocampus, and neocortex in cases of AD, are comprised of dystrophic neurites (abnormal nerve extensions) in proximity to deposits of highly fibrillogenic 42 amino acid A β peptides (A β 42) that aggregate into β -pleated sheets. Deposition of A β in the neural parenchyma occurs early and selectively in AD. A β peptides are derived from β -amyloid precursor proteins (APPs) and generated by the concerted actions of as-yet unidentified proteolytic activities, termed " β -secretase" and " γ -secretase." These A β deposits likely act to recruit additional proteins, including α_1 -antichymotrypsin, components of the complement cascade, and apolipoproteins, and these complexes may attract astrocytes and microglial cells that are often conspicuous around plaques.

Over the past 5 years, we have witnessed an explosion of information pertaining to the accuracy of clinical-pathological diagnoses, genetic risk factors, mechanisms of disease, and potential therapeutic strategies. The contributors to this Perspectives series on AD highlight the extraordinary advances in these arenas and offer perspectives for future investigations in the field.

Early diagnosis and classification

AD is usually classified on the basis of criteria formulated by the NINCDS-ADRDA Joint Task Force, and these methodologies provide highly reliable clinical diagnoses that are confirmed at autopsy. From the point of view of therapeutic intervention, however, it would be highly desirable to recognize individuals at the earliest stages of AD so that maximal benefit might be obtained from agents shown to exhibit therapeutic efficacy. In this issue of the *JCI*, John C. Morris at Washington University School of Medicine offers his Perspective on the distinctions between normal aging and early AD. Morris and colleagues have used a battery of clinical and psychometric measures to establish longitudinal assessments of a large cohort of individuals who showed no detectable cognitive impairment. His clinical assessments, confirmed by quantitative post-mortem studies, support the idea that healthy brain aging is possible even up to the ninth decade. Interestingly, while cognitively normal individuals exhibit minimal neocortical pathology, the extent of the lesions, primarily the burden of SPs, is significantly elevated in

brains of individuals at the earliest symptomatic stages of AD. These findings offer the provocative conclusion that the beginning of AD occurs with the deposition of β -amyloid in the form of large numbers of SPs. He proposes that the presence of SPs exacerbates neurofibrillary degeneration and culminates in neuronal dysfunction and death, which in turn leads to the appearance of clinical symptoms.

Strategies to assess genetic risk for AD

Considering the demographics of the population, we anticipate a profound increase in the prevalence of age-associated disorders, none of which is more dreaded than AD. For the population over the age of 65, epidemiological and genetic linkage studies have uncovered important risk factors for AD. Examples of these phenotypic modifier alleles include apolipoprotein E4 (Apo E- ϵ 4) and a polymorphic α 2-macroglobulin (*A2M-2*) variant; additional genetic risk factors undoubtedly exist. For several years, Rudolph Tanzi and colleagues at Harvard Medical School have employed powerful family-based association studies and statistical approaches to identify genetic risk factors (*A2M-2* among them) in the aging population. In his Perspective in this issue of the *JCI*, Tanzi offers a novel genetic dichotomy model based on the concept that while rare autosomal dominant inheritance of gene mutations causes highly penetrant early-onset form of the disease, the more common forms of AD that occur with advanced age are associated with the genetic risk factors that are distributed throughout the genome in the form of common population polymorphisms (CPPs). The ultimate goal of these studies is to assemble a genotypic profile for each individual that would determine the relative risk of acquiring AD, information that would be critical for making informed decisions regarding the use of potential therapeutic agents and clinical management.

The biology of presenilins in AD

Perhaps the most active area of research in the field over the past 5 years relates to the biology of APP, presenilin 1 (PS1), and presenilin 2 (PS2), membrane proteins that are mutated in pedigrees with early-onset, autosomal dominant forms of Familial Alzheimer's Disease (FAD). In this regard, in vitro and in vivo investigations

have provided compelling evidence to support the view that FAD-linked mutant APP and PS act in a dominant, gain-of-function manner, leading to the overproduction of highly fibrillogenic A β 42 peptides. In his Perspective, which will appear in the next issue of the *JCI*, Gopal Thinakaran at the University of Chicago reviews information that has emerged over the past 4 years pertaining to the normal biology of presenilins and the cellular and physiological consequences of expressing FAD-linked mutant polypeptides. For example, analysis of mice with ablated *PS1* alleles and of lower organisms (*Drosophila* and *Caenorhabditis elegans*) lacking presenilin homologues reveals important roles for these molecules in facilitating Notch signaling and developmental cell fate decisions. In this regard, biochemical and genetic evidence indicates that PS1 plays a critical role in facilitating the proteolytic processing of several membrane proteins, including APP and Notch1. Thinakaran considers several competing models to explain how presenilins facilitate the proteolysis of these diverse substrates, and he suggests experimental strategies that may help resolve this important issue.

Modulation of A β production as a therapeutic strategy

Despite the wealth of evidence supporting the view that A β plays a critical, if not essential, role in the pathogenesis of AD, the reader should be forewarned that the field still remains somewhat divided regarding the role of amyloid deposition in AD pathogenesis. Regardless, the pharmaceutical industry is heavily invested in developing programs aimed at attenuating production and/or aggregation of A β peptides. In the next issue of the *JCI*, Steve Wagner at SIBIA Neurosciences Inc. provides an overview of therapeutic strategies focused on inhibiting A β peptide formation by modulating the still ill-defined β - and γ -secretase activities. Wagner outlines strategies to design molecules that are effective in inhibiting A β production in cell-based assays, as well as methods to validate the in vivo efficacy of these compounds in transgenic animals that overexpress wild-type or mutant human APP. Those compounds that prove efficacious in reducing A β production and amyloid burdens in transgenic mice will no doubt be introduced promptly into people with AD.