Alzheimer Disease: Scientific Breakthroughs and Translational Challenges

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CME Activity

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Learning Objectives: On completion of the article, you should be able to (1) recognize the basis for the amyloid hypothesis about the pathogenesis of Alzheimer disease and current approaches to disease-modifying therapy; (2) differentiate the effect of multiple genetic risk factors identified in genome-wide association studies with the major autosomal dominant forms as well as apolipoprotein E ε4; (3) correlate imaging biomarkers with the pathogenesis of Alzheimer disease; and (4) recognize the extended preclinical course of Alzheimer disease, its neuropathological basis, and its expression in the form of biomarkers.

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In their editorial and administrative roles, William L. Larvie, Jr, MD; Terry L. Joseph; Kimberly D. Slatky; and Nicki M. Smith, MPH, have control of the content of this program but have no relevant financial relationships with industry.

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Abstract

Alzheimer disease (AD) was originally conceived as a rare disease that caused presenile dementia but has come to be understood as the most prevalent cause of dementia at any age worldwide. It has an extended preclinical phase characterized by sequential changes in imaging and cerebrospinal fluid biomarkers with subtle memory decline beginning more than a decade before the emergence of symptomatic memory loss heralding the beginning of the mild cognitive impairment stage. The apolipoprotein E ε4 allele is a prevalent and potent risk factor for AD that has facilitated research into its preclinical phase. Cerebral AB levels build from preclinical through early dementia stages followed by hyperphosphorylated tau-related pathology, the latter driving cognitive deficits and dementia severity. Structural and molecular imaging can now recapitulate the neuropathology of AD antemortem. Autosomal dominant forms of early-onset...
familial AD gave rise to the amyloid hypothesis of AD, which, in turn, has led to therapeutic trials of immunotherapy designed to clear cerebral amyloid, but to date results have been disappointing. Genome-wide association studies have identified multiple additional risk factors, but to date none have yielded an effective alternate therapeutic target. Current and future trials aimed at presymptomatic individuals either harboring cerebral amyloid or at genetically high risk offer the hope that earlier intervention might yet succeed where trials in patients with established dementia have failed. A major looming challenge will be that of expensive, incompletely effective disease-modifying therapy: who and when to treat, and how to pay for it.

Much has changed since November 3, 1906, the day Alois Alzheimer first presented the unusual case of Auguste Deter to the Society of Southwest German Psychiatrists. Her symptoms of delusional jealousy, paranoia, and memory loss began insidiously at the age of 51, ended with her death at age 55, and led to the original conception of Alzheimer disease (AD) as a rare cause of presenile dementia. The first major change occurred 70 years later when Katzman2 and Terry3 argued that the disease bearing Alzheimer's name was also the cause of senile dementia in the elderly, a much more prevalent condition, and so far from previous conceptions AD came to be understood as highly prevalent, the major cause of dementia at any age, and a major cause of death. A second and more recent major change has been to dispel the notion that AD can only be confirmed at autopsy. Advances in brain imaging have made ante-mortem confirmation a reality (within the research arena). Genomics and many more advances have further led to our current concept of AD and constitute the bulk of this review.

CLINICAL BACKGROUND
When symptoms first become apparent, patients are forgetful but still functioning independently. The diagnostic term mild cognitive impairment (MCI) was originally introduced to define a nondisabling but progressive monosymptomatic amnestic syndrome and evolved into a broader classification of early, nondisabling cognitive deficits. Longitudinal studies of patients with MCI have shown that approximately 10% to 15% of patients per year lose their ability to function reasonably independently, the defining characteristic of dementia. After 5 years, about half of all patients with MCI will meet criteria for dementia, particularly AD, and after 10 years, most will have AD or another dementia syndrome. At autopsy, 70% to 80% of patients who originally received a diagnosis of MCI prove to have AD as the major component of the dementia.

The latest version of the National Institute on Aging Alzheimer's Disease Center's Uniform Data Set characterizes AD dementia as an "amnestic multidomain dementia syndrome," meaning progressive memory loss over months to years with the gradual emergence of executive, language, visuospatial, and other deficits with or without behavioral features such as sundowning and paranoia. Diagnostic criteria are summarized in Table 1. Alzheimer disease does not always follow the canonical neuropathological pattern, however. Variant syndromes reflect a different pathological topography. Visual variant AD or posterior cortical atrophy reflects progressive visual impairment related to early degenerative involvement of visual cortices. Other focal variants of AD affect language, motor, and executive functions.

NEUROPATHOLOGY
Neuropathologically, AD is characterized by 2 hallmark features: amyloid plaques and neurofibrillary tangles (NFTs) (Figure 1). Morphologically, amyloid plaques are described as either diffuse or neuritic. Both types may be seen in individuals without dementia, in whom they may indicate an increased risk of progression to dementia. Neuritic plaque is associated with cognitive impairment, whereas for diffuse plaques this relationship is tenuous. The primary event in plaque formation is the deposition of insoluble Aβ amyloid, whereas the "neuritic" elements
TABLE. 1. National Institute on Aging-Alzheimer’s Association Diagnostic Guidelines for Alzheimer Disease

1. Criteria for “all-cause dementia” include cognitive or behavioral symptoms that
(a) interfere with the ability to function at work or at usual activities
(b) represent a decline from a previous level of functioning and performing
(c) are not explained by delirium or major psychiatric disorder
(d) cognitive impairment is detected and diagnosed through a combination of
   i. history from patient and reliable informant and (ii) objective cognitive testing
(e) cognitive/behavioral impairment involves at least 2 domains: memory, executive, visualspatial, language, and/or personality

2. Criteria for probable Alzheimer disease dementia include criteria for all-cause dementia plus
(a) gradual onset over months to years
(b) clear-cut worsening of cognition by report or observation
(c) initial and most prominent deficits are
   i. memory (most common)
   ii. nonamnestic (with deficits in other cognitive domains as well)
   language (logopenic/word finding)
   visuospatial
   executive

3. Criteria for probable Alzheimer disease dementia with “increased level of certainty”
(a) documented cognitive decline (longitudinal cognitive testing)
(b) causative genetic mutation (APP, PSEN1, and PSEN2)

4. Criteria for possible Alzheimer disease dementia
(a) atypical course (e.g., rapid onset) or
(b) etiologically mixed presentation/features of other diseases

5. Probable Alzheimer disease dementia with evidence of the pathophysiological process
   biomarkers

6. Possible Alzheimer disease dementia with evidence of the pathophysiological process
   biomarkers

7. Pathophysiological proved Alzheimer disease dementia (neuropathologically confirmed)

8. Dementia unlikely to be due to Alzheimer disease
   (a) does not meet clinical criteria for Alzheimer disease dementia and/or
   (b) has evidence of a different disease
   (c) both Aβ and neuronal injury markers are negative

Data from Alzheimer’s Dement. 13

(dystrophic axons and dendrites) are a reaction to this and contain pathological bundles of tau proteins that are identical to the NFTs found within neuronal perikarya. Tau is a cytoskeletal protein whose function is to stabilize microtubules that comprise the neuronal cytoskeleton. Tau within dystrophic neurites and NFTs is abnormally phosphorylated. This may impair microtubule binding and facilitate aggregation of tau into paired helical filaments, which are likely to impair the neuron’s ability to maintain extensive dendritic and axonal arborizations, ultimately leading to loss of synaptic connectivity and neuronal death.

Because both plaques and tangles can also occur in individuals without dementia, their mere presence is insufficient to diagnose AD, and so neuropathological criteria have been developed to define the likelihood that dementia is a consequence of AD. In 1985, the recommendations of a National Institute on Aging consensus panel focused on neocortical total plaque density as a function of age,19 a recommendation echoed with a focus on neuritic plaques in 1991 by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD).20 Around this time, Braak and Braak21,22 reported that there is a predictable 6-stage march of NFT pathology from paralimbic to neocortical regions summarized, from earliest to latest, as transentorhinal (stage I/II), limbic (stage III/IV), and neocortical (stage V/VI). In 1997 a National Institute on Aging and Reagan Institute Working Group23 combined CERAD amyloid plaque score and Braak NFT stage to define the likelihood that dementia results from AD. High likelihood is reflected by frequent CERAD neuritic plaque score and Braak NFT stage V/VI; intermediate likelihood by moderate CERAD plaque score and Braak NFT stage III/IV; and low likelihood AD by low CERAD plaque score and Braak NFT stage I/II.23 Essential areas to be sampled differ somewhat between criteria but all include limbic, neocortical, and subcortical areas.

Amyloid plaque distribution, in contrast to NFTs, begins in neocortical regions, and even in the earliest dementia stages it has usually progressed to involve diencephalic regions.24 It continues to build through Braak stages IV and V with progressively increasing subcortical and eventually brainstem and cerebellar involvement, but the rate of deposition may decline in the late stages of dementia.25 As will be discussed, molecular imaging in living patients with positron emission tomography (PET) ligands for amyloid and tau has made it possible to exhibit this neuropathological evolution in real time.

At autopsy, AD is often found not to be a unitary neuropathological diagnosis but includes prevalent comorbidities, particularly vascular and Lewy body pathology, which may contribute to dementia severity.26-31

Table 2 presents the commonly identified major neuropathological comorbidities from the Banner Sun Health Research Institute Brain Bank.32 The proportion of patients with
relatively pure AD decreases from 38% in sexagenarians to 25% in nonagenarians. This heterogeneity is also seen in patients dying during the MCI stage. Even in those older patients who come to autopsy without cognitive problems, AD, vascular, and Parkinson disease-related pathologies are frequent findings (Table 3).

CLINICAL NEED
A total of 5.4 million Americans and 44 million people worldwide have AD, and with the aging population, incidence and prevalence figures are expected to double by 2050. In comparison to whites, the relative risk of dementia is twice that in African Americans and 1.5 times that in Hispanic Americans, mainly related to contributory factors such as cardiovascular disease and diabetes, as well as a higher prevalence of apolipoprotein E (APOE)ε4 allele in African Americans. Incidence rates for the age groups (in years) 65 to 74, 75 to 84, and 85 and older are 2, 13, and 37 cases per 1000 people per year, respectively, with a lifetime risk for those aged 65 years and older of 9% for men and 17% for women.

To place recent challenges and developments in context, consider that the January 23, 2014, issue of the New England Journal of Medicine contained 2 back-to-back articles that disappointed a field that anticipated nothing less than a potential cure for AD on the basis of a wealth of evidence that immunotherapy against Aβ amyloid should halt disease progression, yet failed. For the past 25 years, the amyloid hypothesis, which simply stated, posits the accumulation of Aβ amyloid in the brain as the inciting event that triggers neurodegeneration causing AD, has been the prevailing paradigm for AD pathogenesis, and has therefore guided the development of disease-modifying treatments. Evidence supporting the amyloid hypothesis is strong. Amyloid accumulation begins early in the disease process, and dominantly inherited AD (DIAD) can be caused by highly pathogenic variants in any of the 3 genes, all of which affect cerebral amyloid production or aggregation including the amyloid precursor protein (APP) gene, presenilin 1 (PSEN1), and presenilin 2 (PSEN2). The PSEN1 and PSEN2 encode the active site of γ-secretase, a key enzyme that leads to the production of Aβ fragments.

### TABLE 2. Decadal Counts of Neuropathological AD Total Comorbidities From Banner Sun Health Research Institute Brain and Body Donor Program/Arizona Study of Aging and Neurodegenerative Disorders

<table>
<thead>
<tr>
<th>Decade</th>
<th>AD “pure”</th>
<th>AD all</th>
<th>AD/VAAD</th>
<th>AD/PD</th>
<th>AD/DBL</th>
<th>AD/PSP</th>
<th>AD/HS</th>
<th>AD/FTLD-TDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>50s-60s</td>
<td>20 (38%)</td>
<td>53</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>70s</td>
<td>55 (33%)</td>
<td>177</td>
<td>14</td>
<td>23</td>
<td>33</td>
<td>45</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>80s</td>
<td>90 (26%)</td>
<td>350</td>
<td>45</td>
<td>33</td>
<td>54</td>
<td>128</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>90s</td>
<td>35 (25%)</td>
<td>138</td>
<td>38</td>
<td>6</td>
<td>20</td>
<td>44</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>100s</td>
<td>1 (14%)</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

AD = Alzheimer disease; AD/LBD = Alzheimer disease with Lewy body disease insufficient for diagnosis of either Parkinson disease or dementia with Lewy bodies; DLB = dementia with Lewy bodies; FTLD-TDP = frontotemporal lobar degeneration with TDP-43 proteinopathy; HS = hippocampal sclerosis; PD = Parkinson disease; PSP = progressive supranuclear palsy; TDP = TAR DNA binding protein; VaD = vascular dementia.

Categories with mixed diagnoses are not mutually exclusive. Note that AD “pure” does not exclude comorbid minor neuropathological diagnoses.

AD “pure” is defined as AD without any of the other listed diagnoses. AD was defined as a clinically documented dementia with National Institute on Aging—Reagan Institute Working Group intermediate or high AD pathology.
that are susceptible to aggregation and plaque formation. Furthermore, although most APP variants are pathogenic, one has been described that actually protects against AD by reducing β-secretase 1 cleavage and so Aβ production. 

**SCIENTIFIC BACKGROUND**

The normal roles of APP and amyloid in the brain are far from well understood but shed further light onto their potential role in AD pathogenesis. The APP gene is ancient. The ancestral gene is present in invertebrates, and the amyloidogenic sequence that predisposes to AD is found in all vertebrates. Knockouts of the APP gene and its homologues in mice are lethal. In a zebrafish model, knockdown of APP results in a deformed fish that is restored by wild-type human APP but not the AD-related Swedish mutation APP. In postnatal humans, neurogenesis involves approximately a third of hippocampal neurons (including most neurons in the dentate gyrus) at a rate of 700 new neurons in each hippocampus per day, corresponding to an annual turnover of 1.75% within the renewing fraction (0.004% of dentate gyrus neurons daily). By contrast, 51% of nonneuronal cells turn over annually at a rate of 3.5% per year. There is a decline with aging, and the degree of ongoing neurogenesis in the adult human brain is still debated. (A recent estimate indicates that the rates of adult neurogenesis in the subventricular and subgranular zones approach that of the surrounding parenchyma and reflect microglia rather than neurons).

In the nonamyloidogenic (normal aging) pathway, APP is cleaved mostly within the plasma membrane by γ-secretase within the Aβ region (destroying the Aβ sequence) releasing a soluble fragment, sAPPα (or Aβ1–40), to the extracellular space. γ-Secretase includes members of the ADAM (a disintegrin and metallocproteinase) family, ADAM10 and ADAM17. In the brain, sAPPα levels are particularly high in the subventricular zone, 1 of 2 areas of neurogenesis, and sAPPα is an essential proliferation factor for neural and nonneural adult stem cells.

In the amyloidogenic pathway that leads to AD, APP is first cleaved instead by β-secretase 1, releasing sAPPβ to the extracellular space sAPPβ drives stem cells toward neural differentiation. sAPPα and sAPPβ are normally produced in a 9:1 ratio and together stimulate neural stem cell proliferation and differentiation. The remaining membrane-bound C terminal APP (C99) is subsequently cleaved by γ-secretase, releasing the insoluble Aβ1–42 peptide (and the APP intracellular domain) (Figure 2). Synaptic activity results in the release of Aβ1–42 peptide into the extracellular space, driving aggregation. Insoluble Aβ1–42 aggregates into plaques and is thought to trigger tau hyperphosphorylation, although currently it is unknown how that occurs. The result, however, leads to the loss of...
cytoskeletal structure, dendritic spines, axonal degeneration, synaptic connectivity, and neuronal death.

More recently it has been shown that Aβ amyloid may have antimicrobial properties. In animal models, Aβ oligomers bind to microbial cell walls, inhibit their adhesion to host cells, and mediate agglutination and eventual entrapment of microbes. Aβ deposition is accelerated and colocalized with invading bacteria, suggesting that Aβ deposition in AD may reflect dysregulation of the brain's innate immune system responding to microbial or sterile inflammatory stimuli. Triggering Receptor Expressed on Myeloid cells 2 (TREM2) is a microglial surface receptor that has also been linked to AD susceptibility. TREM2 deficiency enhances Aβ accumulation, as dysfunctional microglia fail to cluster around Aβ plaques and become apoptotic. Together, these findings raise the possibility of a role for innate immune dysregulation in AD pathogenesis.

Tau is a microtubule stabilizer that is dynamically phosphorylated and dephosphorylated to allow it to dissociate from microtubules during cellular mitosis. In 2009, Clavaguera et al found, in a transgenic mouse model, that hyperphosphorylated filamentous tau can spread from neuron to neuron in a prion-like fashion, taken up by neighboring neurons by bulk endocytosis. They subsequently reported that human tau from the brains of patients with progressive supranuclear palsy and related tauopathies, when injected into the brains of transgenic mice, also spread in a prion-like fashion. It has since been shown that amyloid too may spread in a prion-like fashion in human brains, but there is currently no evidence of human-to-human transmission.

CHALLENGES AND PITFALLS
Immunomodulatory strategies for AD were introduced by Schenk et al in 1999 through the demonstration that active immunization of transgenic mice (containing the human APP mutation) with Aβ amyloid prevented the formation of amyloid plaques if immunized when young and reduced pathological burden if immunized when old (and pathology had already developed). This was considered a major discovery and development of human trials proceeded in an expedited fashion. The initial human active immunization trial (AN-1792) resulted in the unexpected occurrence of autoimmune meningoencephalitis with associated cerebral edema in 6% of participants bringing the trial to a halt. Subsequent neuropathological examinations revealed evidence of patchy plaque removal (but equivocal effect on the overall Aβ load), generally supporting the concept of an immunomodulatory approach and leading ultimately to the launch of passive immunization strategies. Bapineuzumab and solanezumab are monoclonal antibodies directed against epitopes of Aβ amyloid. Passive immunization strategies with these agents were shown to engage their molecular targets with improvement in surrogate biomarkers, yet neither reduced the rate of cognitive or functional decline in symptomatic cohorts. A subsequent secondary analysis of those patients in the solanezumab trial with only mild stage AD appeared to show a 34% reduction in the rate of progression over 18 months, but recently reported results from a phase 3 trial in mild stage AD failed to achieve a similar outcome. The relative lack of efficacy of this highly strategic
Verbal memory (brown), 3.

Test of memory (AVLT) score in 84 homozygotes (apoEε4), heterozygotes (orange), and noncarriers (brown), illustrating apoEε4 gene dose-related preclinical decline in memory performance in ε4 carriers.

**FIGURE 3.** Porcupine plots of longitudinal memory performance on the Auditory Verbal Learning Test (AVLT) long-term memory score in apolipoprotein E ε4 homozygotes (blue), heterozygotes (orange), and noncarriers (brown), illustrating apoEε4 gene dose-related preclinical decline in memory performance in ε4 carriers.

[Graph showing memory performance over age]

An approach has caused intense reconsideration of current disease models, trial design, and diagnostic and therapeutic approaches. Progress in light of these setbacks has led to a greater understanding of AD's extended preclinical phases; the development of imaging and biofluid biomarkers for earlier detection and tracking of disease progression, especially before the onset of symptoms; and the complex genomics of AD with the hope of identifying new therapeutic targets.

The conclusion reached by many in reaction to the failed immunotherapy trials was that interventions were “too little too late,” but that success might yet be achieved if treatment was initiated earlier in the disease course. The earliest stages of AD are characterized by amyloid deposition and followed later in the disease course by tau pathology. By the time mild to moderate dementia stages are reached, amyloid levels have essentially plateaued and deficits are driven by the progressive tau pathology. Intervention at the dementia stage therefore could well be too late if amyloid is no longer driving the disease process. Tau pathology is primarily intracellular and so would seem to be a less viable immunotherapy target, although passive immunization strategies in mouse models have shown encouraging effects in limiting AD spread. Although cerebral amyloid levels build, patients remain largely asymptomatic. Designing a clinical trial for an asymptomatic cohort requires some understanding of the preclinical phase as well as surrogate disease biomarkers that can be tracked so as to assess potential therapeutic efficacy.

**POSSIBLE SOLUTIONS**

Evidence for a preclinical phase of AD, a time when AD pathology is building yet no symptoms are evident, originally came from autopsy studies of elderly patients who appeared clinically healthy yet harbored moderate degrees of AD pathology in their brains. With the discovery that the apoEε4 allele is a prevalent and powerful genetic risk factor for AD, such preclinical pathology was found to correlate with apoEε4. Among apoEε4 carriers dying of unrelated causes in their 50s, approximately 40% harbor AD relevant pathology in the form of either amyloid plaques or medial temporal NFTs, and autopsy studies of elderly apoEε4 carriers without dementia has shown that they harbor higher amyloid levels in cerebral parenchyma and vasculature than apoEε4 noncarriers.

Fluorodeoxyglucose (FDG)—PET studies of asymptomatic apoEε4 carriers in their 50s reveal metabolic patterns resembling AD. Volumetric magnetic resonance imaging (MRI) studies report accelerated hippocampal atrophy in advance of MCI diagnosis, and longitudinal neuropsychological studies report accelerated memory decline beginning in the mid to late 50s and early 60s, an estimated 10 to 15 years in advance of MCI symptoms. Evidence from the Nun study suggested that preclinical changes may exist even during young adulthood, supported by imaging, and some neuropathological evidence as well. Possibly such early differences are developmental rather than early-stage AD, a possibility indirectly supported by subtle neuroanatomical differences found in apoEε4–positive infants.

With the advent of amyloid ligands suitable for PET, it has become possible to noninvasively exhibit that cerebral amyloid increases with age and is accelerated in a gene-dose fashion by apoEε4. Such studies are now being incorporated into trial design to address another possible reason for previous therapeutic failures: up to a third of apoEε4 noncarriers with clinically diagnosed
AD lack significant amounts of cerebral amyloid, thus implying that they lack the target for an immunotherapeutic agent. Recently published results of a phase 1 trial of adaucimab, a human monoclonal antibody that selectively targets aggregated Aβ, in which all patients enrolled were required to have exhibited cerebral amyloid on PET scans reported the wisdom of this approach by achieving robust dose- and time-dependent amyloid clearing and even a hint of possible cognitive benefit.

These preclinical data were synthesized into operational research criteria for preclinical AD in 2011 that defined the stages of asymptomatic cerebral amyloidosis followed by neurodegeneration and finally preclinical cognitive decline. Further refinement of the preclinical AD concept came from Jack et al., who used a combination of amyloid and neurodegeneration biomarkers, specifically amyloid PET and volumetric MRI, respectively, to describe 4 possible stages for preclinical AD: stage 0 (amyloid negative, neurodegeneration negative), stage 1 (amyloid positive, neurodegeneration negative), stage 2 (amyloid positive, neurodegeneration positive), and suspected non-Alzheimer pathology (amyloid negative, neurodegeneration positive), the pathological basis of which is likely heterogeneous and largely composed of age-associated tauopathy and cerebrovascular and Lewy body pathology.

The Dominantly Inherited Alzheimer Network is a multicenter study pooling members from kindreds with differing genetic backgrounds that share a disease-causing autosomal dominant mutation. Individuals carrying one of the known DIAD mutations offer the advantage that the age window of expected symptomatic onset (within a kindred) is known, allowing investigators to time presymptomatic biomarker and cognitive change. The Dominantly Inherited Alzheimer Network has shown that biomarker changes follow a sequence with the earliest change being declining cerebrospinal fluid (CSF) Aβ amyloid levels occurring as much as 25 years in advance of predicted symptomatic onset, followed by increasing CSF tau, accelerated cortical atrophy on MRI, declining cerebral metabolic glucose rates on FDG-PET, falling memory scores, and finally falling mental status test scores 5 years before symptoms begin. Analogous results were observed in a large Colombian kindred harboring a PSEN1 mutation. Both cohorts have become the focus of secondary prevention trials using agents that target amyloid.

**Biomarkers**

Biomarkers reflect disease-specific pathology that may appear before the onset of clinically evident symptoms. Imaging and CSF biomarkers in particular have made possible the exposition of disease-specific pathology in real time, and although not currently recommended for most clinical purposes, they have revolutionized preclinical diagnosis, disease tracking, and clinical trial design (Figure 4).

**Magnetic Resonance Imaging.** Medial temporal NFT pathology underlies the amnestic syndrome that characterizes AD. Hippocampal volume declines early in patients with AD and progresses in parallel with dementia severity, an observation that led to pioneer hippocampal volumetry as perhaps the first readily accessible AD biomarker. Since its initial descriptions, it has been included in the multicenter Alzheimer’s Disease Neuroimaging Initiative, and commercially available adaptations have been derived that are now available for clinical application. More recent recommendations from Kropman et al. are that cortical/gray-matter thickness may be a more consistent, age-independent AD biomarker in contrast to hippocampal volumes that must account for age-specific norms and head size. Many other MRI-based techniques are used including ventricular volume, white matter tract integrity (diffusion tensor imaging) resting state functional MRI, and activation paradigm-based functional MRI that all share the general principle of progressive decline in cerebral anatomy and functional integrity reflecting AD progression.

**Molecular Imaging.** A little over a decade ago, Klunk et al. described the first human trial of an amyloid ligand adapted for PET termed Pittsburgh compound B that imaged a key molecular component of AD in living patients, Aβ amyloid. Its short half-life limited its general accessibility and spurred the
development of amyloid ligands with longer half-lives that make them more accessible to medical centers lacking the ability to generate radiopharmaceuticals. All have been validated for the detection of moderate or frequent neuritic plaques by large antemortem-postmortem correlation studies. Clinical interpretations of amyloid scans are dichotomized into positive or negative depending on the relative cerebral amyloid burden compared with the cerebellum (an area typically spared by AD), but amyloid accumulation is detectable preclinically. Correlations between cerebral amyloid levels or its topographical distribution and cognitive deficits have been weak. More recently, tau PET has entered into research applications and topographical patterns of ligand distribution correlate well with clinical deficits. Taken together, amyloid and tau imaging essentially recapitulate in living patients the major neuropathology of AD.

**Metabolic Imaging.** Fluorodeoxyglucose-PET typically reveals reduced cerebral metabolic glucose rates in parietal, lateral temporal, and posterior cingulate cortices in patients with AD. Analyzing FDG-PET images from 146 patients with mild to moderate dementia who were subsequently followed for at least 2 years and 139 patients who had postmortem neuropathological assessments an average of 3 years later, FDG-PET readings were associated with approximately 93% sensitivity and 75% specificity in predicting subsequent clinical decline and the neuropathological diagnosis of AD. On the basis of these and other findings, the US Centers for Medicare & Medicaid Services determined that FDG-PET is reasonable and necessary in patients with documented cognitive decline and a recently established diagnosis of dementia who meet clinical criteria for both AD and frontotemporal dementia, who have been evaluated for specific alternate neurodegenerative diseases or causative factors, and for whom the cause of the clinical symptoms remains uncertain (Decision Memo CAG-00088R, September 15, 2004).

**Cerebrospinal Fluid.** With disease progression, soluble Aβ amyloid aggregates into insoluble amyloid plaques, raising brain amyloid levels while reducing soluble CSF levels. As neurons die, total and phosphorylated tau is released into the CSF, raising tau levels. Cerebrospinal fluid total tau, phosphotau, and Aβ reliably distinguish patients with AD from
controls.\textsuperscript{111} Serial sampling of CSF within individuals has shown that CSF Aβ levels fluctuate over the day in a sinusoidal fashion. Average maximum values are 200\% those of minimum values.\textsuperscript{112} Differences between diagnostic laboratories have also resulted in high variability in CSF biomarker levels, highlighting the need for standardization.\textsuperscript{117} Plasma levels of Aβ have been less reliable in distinguishing patients and controls, possibly owing to peripheral production of Aβ. Plasma levels of total tau distinguished the groups better, but significant interstudy variability makes this unreliable presently as a diagnostic test.\textsuperscript{111}

\section*{Genomics}

Genes can inform disease susceptibility, and in symptomatic patients, they confirm the specific genetic basis for a familial disease. Freer et al\textsuperscript{114} recently reported that genomics can inform tissue vulnerability as well. They reported genomic profiles of brain regions related to Aβ and tau aggregation in a composite vulnerability score and found that brain regions with higher scores (greater vulnerability) closely matched Braak NFT stage.

\section*{Mendelian Forms}

Dominantly inherited AD can be caused by rare autosomal dominant variants in the APP,\textsuperscript{40} PSEN1,\textsuperscript{41} and PSEN2\textsuperscript{42} genes, which together account for approximately 5\% to 10\% of young-onset AD. Of the 39 APP mutations reported to date in 93 families, all shift APP proteolysis toward Aβ\textsubscript{42} production, resulting in greater amyloid aggregation.\textsuperscript{115} Patients with Down syndrome (trisomy 21) have an extra copy of the APP gene resulting in greater Aβ production and consequently fibrillar amyloid deposition.\textsuperscript{116} If a patient with Down syndrome lives beyond the age of 40 years, there will be neuropathological evidence of AD at autopsy. Progressive dementia increases with age and peaks at approximately 40\% to 75\% over the age of 60. Analysis of the amyloid plaques has revealed that trisomy 21 predisposes to larger plaques, presumably reflecting increased production of Aβ amyloid.\textsuperscript{117} The PSENI\textsuperscript{\textdegree}s encode the active site of γ-secretase,\textsuperscript{13} leading to the production of insoluble Aβ amyloid that is susceptible to aggregation and plaque formation. PSEN1 is the most prevalent of the autosomal dominant mutations, and PSEN2 mutations are the least prevalent. In PSENI DIAD, mutant γ-secretase results in longer aggregation-susceptible peptides.\textsuperscript{118}

\section*{Apolipoprotein E}

The APOE\textsubscript{4} allele located on chromosome 19 accounts for more cases of AD than any other. It is associated with late-onset familial and "sporadic" AD affecting both overall disease risk and age of onset with a generally deleterious gene-dose effect of ε4 and protective effect of ε2.\textsuperscript{12,13} Prevalence varies worldwide from approximately 5\% to 10\% in Mediterranean and Asian regions to approximately 30\% in parts of northern Europe (and ~23\% in North America).\textsuperscript{119,120} Overall, AD risk is increased 3- to 4-fold in APOE\textsubscript{4} heterozygotes and 14-fold in APOE\textsubscript{4} homozygotes, with some variance depending on age, sex, and race.\textsuperscript{121} Whether there is a single key effect of APOE is unclear, but both amyloid (eg, enhanced aggregation and reduced clearance) and non-amyloid (eg, neurotoxic carboxyl fragments and enhanced tau phosphorylation) effects have been described.\textsuperscript{122} APOE does not follow typical Mendelian patterns of disease causation, but has been proposed to represent a low penetrant autosomal semidominant form on the basis of absolute disease risk estimates.\textsuperscript{123} An additional controversy is the potential contribution of the gene for translocase of the outer mitochondrial membrane (TOMM40) to AD risk. TOMM40 is adjacent to APOE on chromosome 17 and has been proposed by Roses et al\textsuperscript{24} to contribute to AD risk and possibly may account for some of the risk attributed to APOE itself.

\section*{Non-Mendelian Forms}

For expansion of gene symbols in this section, see www.genenames.org. With the advent of large-scale genome-wide association studies, the number of genetic associations with AD risk has accelerated. Unlike Mendelian inheritance, or even APOE, the effect of each such variant is low. If a single copy of the APOE\textsubscript{4} allele increases AD risk by 300\% to 400\%, the effect of the "genome-wide association study" variants averages 10\% to 25\%, though they are higher for some.\textsuperscript{126} Population surveys find that these variants occur in clinically unaffected individuals as well as those with AD. Some affected genes lend themselves to pathway
categorization, including cholesterol metabolism (eg, APOE and ABCA7), intracellular vesicle trafficking (eg, SORL1 and ABCA7), synaptic/membrane function (eg, PICALM, BIN1, and EphA1), innate immunity (eg, TREM2, CR1, and CD33), and of course Aβ metabolism (eg, APP, PSEN1, and PSEN2). It is an attractive concept but fraught with challenges. Not all genes lend themselves to simple functional categorization. A gene's known major function may be disturbed, yet the resulting disease may result from an unrelated and unknown effect. A single variant might be classified as benign owing to its prevalence in the healthy population, but a single gene can harbor multiple benign variants whose cumulative effect is unknown. Nonetheless, given the heritability of AD, it seems likely that some combination of variants explain disease susceptibility, age of onset, progression rate, and other phenotypic differences.

UNRESOLVED CLINICAL QUESTIONS: DIAGNOSIS

The overriding principle of diagnosis remains the exclusion of reversible mimics. To that end, a standard clinical evaluation includes a thorough history and physical examination, structural brain imaging, basic laboratory studies, and cognitive assessment that may be an office-based Brief Mental Status Examination or detailed neuropsychological assessment to establish the quality and severity of the cognitive syndrome. Spinal fluid examination, electroencephalography, and many other tests are possible, depending on individual circumstances. The main controversies in diagnosis are the utility of genetic and biomarker tests.

Genetic counseling and testing (for APP, PSEN1, and PSEN2) should be offered to any patient or family with suspected DIAD. Typically the age of onset in these cases is below 60 years, and there is usually a strong family history of dementia on 1 parent's side. Identification of the causative mutation in the patient offers the chance to test first-degree relatives, and particularly children who may alter their life plans depending on their understanding of their own disease risk and expected age of onset. APOE testing is another story. The negative predictive value of APOEε4 is low, so its absence does not rule out AD, but the presence of an APOEε4 allele in a patient with dementia has high positive predictive value for a diagnosis of AD.125 APOE status does not affect the therapeutic alternatives for a patient with dementia or their family members in the way that DIAD genes do. Therefore, although APOE testing is possible, it is not currently recommended for routine clinical purposes.126

Biomarker tests are not generally useful for identifying potentially reversible mimics, but they may enhance diagnostic certainty,106 especially in patients with clinically atypical presentations, and there are a few scenarios in which they can be particularly helpful. For example, a young patient still working becomes disabled by memory loss and needs positive proof of AD, not simply tests that "rule out" other causes. Another example is that of a patient being considered for ventriculoperitoneal shunting for suspected normal pressure hydrocephalus. Alzheimer disease is the most frequent reason for therapeutic failure,127 so a biomarker test indicating the presence of AD pathology may help avoid unnecessary surgery. Whether an older patient with clinically probable AD should also undergo biomarker testing to further enhance diagnostic confidence is less clear. Biomarker tests add substantially to the cost of the evaluation and have only a minor effect on therapeutic decisions.128

More controversial is the utility of presymptomatic testing. Many people express a desire for such testing even in the absence of an effective therapy. The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study has examined the effect of APOE genotype disclosure on healthy volunteers. The main message of the REVEAL study has been interpreted to be that disclosure can be done safely,129 but the careful screening and follow-up used by the REVEAL study is unlikely to accompany widespread clinical practice and does not now accompany direct-to-consumer marketing. In the absence of such a best practice, respondents to an Internet-based survey generally endorsed positively adaptive reactions (such as leading a healthier lifestyle and obtaining long-term care insurance) to "bad news," but more than 18% endorsed spending all their money and approximately 11% endorsed consideration of suicide. Responses were similar for
biomarker testing. With the advent of pre-symptomatic trials as well as the commercial availability of genetic tests, such testing is happening, despite these caveats.

UNRESOLVED CLINICAL QUESTIONS:

THERAPY

In the absence of disease-modifying therapy, the overriding principle of treatment is maximizing quality of life through symptom management. A systematic approach that considers prevention (or mitigation of symptom progression), intellectual impairment, behavioral problems, sleep disorders, commonly associated problems (eg, parkinsonism), abrupt or unexpected clinical decline, and lifestyle issues (particularly driving, weapons, advanced directives, and assisted living/extended care) are all part of Good Clinical Practice. Medications that are specifically identified as AD therapy are limited to the cholinesterase inhibitors, and the N-methyl-D-aspartate receptor antagonist memantine. All cholinesterase inhibitors are Food and Drug Administration (FDA) approved for the treatment of mild to moderate stages of dementia caused by AD, and memantine is FDA approved for the moderate to late stages of AD. An unresolved question is when to discontinue them, but the decision is typically individualized according to a family’s wishes.

With regard to AD prevention and the mitigation of symptom progression, there is no level I evidence for a neuroprotective effect for anything despite television advertisements claiming such and numerous news stories generally extrapolated from animal model or epidemiological findings. There is, in fact, level I evidence against protective effects for nonsteroidal anti-inflammatory drugs, estrogen replacement therapy in women, vitamin E, vitamin B-mediated homocysteine lowering, Ginkgo biloba, statins, and other agents as well. Epidemiological evidence has supported a modestly protective effect for Mediterranean diet, physical exercise, and recreational cognitive activity against dementia in general, although it is less clear to what extent the effect is specific to AD or cerebrovascular contributions to dementia. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability was a randomized trial of a multidomain intervention combining diet, exercise, cognitive training, and vascular risk monitoring, and it reported a modestly protective effect against cognitive decline in this elderly cohort. Similarly, lower educational background, intellectually oriented occupations, and related characteristics have been linked to the phenomenon of cognitive reserve in which greater intellectual attainment seems to mitigate the adverse effect of dementia pathology. However, cognitive reserve proxies have been shown to primarily affect cerebrovascular components of dementia, and when a developmental proxy (sex-based memory advantage) is used instead, there does not appear to be any mitigation of preclinical memory decline.

Of the various behavioral problems experienced by patients with dementia, the most problematic are agitation and psychosis. There are no agents that have received FDA approval for the specific treatment of agitation or psychosis in patients with AD (although recently pimavanserin was approved for the treatment of Parkinson disease–related psychosis). In the absence of level I evidence, anecdotal experience and meta-analysis suggest that atypical antipsychotic drugs may be the preferred agents for AD-related agitation, but because they lack FDA approval for such an indication, clinical judgment is essential. Common patterns of usage in a community-based setting as well as more aggressive regimens aimed at higher minimum doses often fail to achieve therapeutic benefit. Furthermore, the FDA has required a black box warning label on the use of atypical antipsychotic drugs in treating patients with dementia because of data suggesting an increased risk of mortality. The “typical” antipsychotic drugs such as haloperidol have a high likelihood of causing or exacerbating parkinsonism or tardive dyskinesia (if used chronically) and confer an even higher mortality risk as compared with the newer atypical neuroleptic drugs.

Perhaps the greatest controversy, however, is one that has not yet materialized, but may be looming: balancing the cost of therapy with efficacy. Immunotherapy trials involving monoclonal antibodies have failed to halt AD progression, but with earlier intervention, agents targeting different epitopes, and other factors, it seems quite possible
that one day such an agent will achieve statistical significance in its primary end point. If we may infer the potential cost of these agents from their counterparts in the oncological realm, they are going to be expensive, ranging in the tens of thousands of dollars annually, and quite possibly resulting in a national cost that exceeds the current total dementia care cost of more than $200 billion annually. If such an agent fails to halt disease progression but only slows it by 10% to 30%, would that justify the cost to society? Should patients with late-stage dementia receive such treatment, or should treatment be limited to those with mild-stage disease? Should taxes be raised to provide the needed supplemental dollars to entitlement programs that may not otherwise be funded to shoulder such a cost given the huge number of patients affected by AD? And if such treatment were preventable, should the 2% of the US population that is an APOE4 homozygote receive treatment, and beginning at what age? What about E4 heterozygotes? What about everyone with Down syndrome and the less common DIAD gene carriers?

CONCLUSION

The challenges raised by AD may be unlike any other disease. When it strikes younger people, it is undeniably a disease. When we find traces of it in the brains of nonagenarians without dementia, we confront its association with normal aging. Our ability to diagnose it is increasing in precision, and our therapies may be getting closer to disease modification, but at a cost. The greatest challenges ahead may lie not in the laboratory or the clinic but in our social conscience and government.

Abbreviations and Acronyms. AD = Alzheimer disease; APOE = apolipoprotein E; APP = amyloid precursor protein; CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; CSF = cerebrospinal fluid; DIAD = dominantly inherited Alzheimer disease; FDA = Food and Drug Administration; FDG = fluorodeoxyglucose; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; NFT = neurofibrillary tangle; PET = positron emission tomography; PSEN = presenilin; REVEAL = Risk Evaluation and Education for Alzheimer’s Disease; TREM2 = Triggering Receptor Expressed on Myeloid cells 2

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REFERENCES

ALZHEIMER DISEASE


