Alzheimer's Disease A Century Later

Richard J. Caselli, M.D.; Thomas G. Beach, M.D.;
Roy Yaari, M.D., M.A.S.; and Eric M. Reiman, M.D.

Received Nov. 18, 2005; accepted Aug. 30, 2006. *From the Department of Neurology, Mayo Clinic and Arizona Alzheimer's Disease Consortium, Scottsdale (Dr. Caselli); the W. H. Civin Laboratory for Neuropathology, Sun Health Research Institute and Arizona Alzheimer's Disease Consortium, Sun City (Dr. Beach); the Banner Alzheimer's Institute and Arizona Alzheimer's Disease Consortium, Phoenix (Dr. Yaari); and the Banner Alzheimer's Institute, Neurogenomics Division, Translational Genomics Research Institute; the Department of Psychiatry, University of Arizona; and Arizona Alzheimer's Disease Consortium, Phoenix (Dr. Reiman), Ariz.*

Supported in part by grants P30 AG19610-01 from the National Institute on Aging and MH057899-06 from the National Institute of Mental Health and by the state of Arizona.

Dr. Reiman has served as a consultant to Eli Lilly, Pfizer, Forest, Intellect Neurosciences, Ceregene, and GlaxoSmithKline; has received grant/research support from National Institute of Mental Health, National Institute on Aging, GlaxoSmithKline, and the state of Arizona; and has a patent pending on the use of imaging in the evaluation of Alzheimer's disease prevention therapies. Drs. Caselli, Beach, and Yaari report no other significant commercial relationships relevant to the study.

Corresponding author and reprints: Richard J. Caselli, M.D., Department of Neurology, Mayo Clinic and Arizona Alzheimer's Disease Consortium, 13400 East Shea Blvd., Scottsdale, AZ 85259 (e-mail: Caselli.Richard@Mayo.edu).

Objective: To provide a current survey of the clinical and pathologic features, known genetic and suggested pathogenic contributions, diagnosis, and treatment of Alzheimer's disease (AD) and related forms of dementia.

Data Sources: PubMed was searched for specific indexing terms identified by the authors as relevant to the topic. Also included were diagnostic and consensus criteria and classic references long standing in the Alzheimer's disease literature.

Data Synthesis: AD is the most common form of disabling cognitive impairment in older persons, and its prevalence is rapidly growing as people live to older ages. Clinically, the disorder is characterized by a gradual but progressive decline in memory and other cognitive domains and the frequent occurrence of noncognitive behavioral symptoms. Neuropathologically, the cardinal features of AD include neuritic plaques, neurofibrillary tangles, and the loss of synapses and neurons. The clinical evaluation of AD includes a history and physical examination, laboratory tests, and structural brain imaging to exclude less common forms of dementia. The clinical management of AD includes medication and nonmedication strategies for addressing cognitive, behavioral, and other commonly associated symptoms of patients as well as lifestyle changes such as driving cessation and residential care. Genetic causes of familial Alzheimer's disease as well as genes that predispose to late-onset and sporadic Alzheimer's disease have led to greater understanding of the pathophysiology of the neurodegenerative process.

Conclusions: While there has been great promise in the scientific understanding, early detection, and tracking of AD and in the discovery of promising disease-slowing treatments, there remains an unmet urgent need to identify effective primary and secondary prevention therapies in order to avert a financially overwhelming public health problem.

(J Clin Psychiatry 2006;67:1784–1800)

November 3, 2006, marks the 100-year anniversary of the 37th Meeting of the Southwest German Psychiatrists in Tübingen, Germany, in which Alois Alzheimer presented a patient with a decline in memory and other cognitive domains, noncognitive behavioral features, and the hallmark neuropathologic findings of senile plaques and neurofibrillary tangles of what later was termed *Alzheimer's disease* (AD). AD is now known to be the most common cause of dementia. It is a severe and common disorder, and its incidence increases with age. With more people living longer, the prevalence of AD is increasing. The number of Americans with AD has doubled since 1980 to 4.5 million and may triple again by 2050.[1] This imposes an immense burden on families as 70% of patients are cared for at home.[2] The cost of care averages $42,000 annually[3,4] and $174,000 over the lifetime of an AD patient,[5] so that reducing the financial as well as medical burden of AD is a major goal of medical diagnosis and management. These figures also do not account for potentially reversible conditions that are mistaken for AD, for lost productivity in the minority of patients with the early-onset form of AD, or for the increased medical burden of caregiver stress-related illness. AD, without question, is the dark cloud on the age horizon, and to avoid drowning in the deluge of problems that it can cause, accurate diagnosis and appropriate management are essential.

WHAT IS ALZHEIMER'S DISEASE?

AD is a degenerative brain disease. It targets specific brain regions early in its course, especially the cholinergic basal forebrain and medial temporal lobe structures including the hippocampus, amygdala, and entorhinal cortex.[6–10] Memory loss therefore results as an early clinical correlate. AD spreads in a characteristic sequence involving posterior cingulate, temporal, and parietal isocortical regions over years. Based on the distribution of these pathologic changes, the characteristic "cortical" clinical features of aphasia, apraxia, and agnosia emerge along with consequent amnesia and personality changes.

MILD COGNITIVE IMPAIRMENT

The clinical symptoms and signs of AD reflect the underlying topography of the disease. Early in the course of AD, patients may not yet be functionally impaired. The diagnostic term *mild cognitive impairment* (MCI) was originally introduced to define a progressive monosymptomatic amnestic syndrome,[11–13] but more recently has evolved by consensus into an entire classification scheme for early, nondisabling cognitive disorders.[14,15] These constitute amnestic MCI–single domain, amnestic MCI–multiple domains, nonamnestic MCI–single domain, and nonamnestic MCI–multiple domains. Each MCI subtype can then be classified according to the presumed etiology—degenerative, vascular, psychiatric, and so forth. *Amnestic MCI* is the originally conceived monosymptomatic amnestic form and is often applied to those with a presumed underlying degenerative etiology. *Nonamnestic MCI–single domain* refers to monosymptomatic syndromes other than memory loss such as anomia, visual disorders, apraxia, executive disorders, or essentially any deficit that can be considered to be confined to a single cognitive domain. Finally, *amnestic* and *nonamnestic MCI–multiple cognitive domains* refer to patients with impairment in multiple cognitive domains with and without memory impairment.

Amnestic MCI is the most specifically correlated with AD,[16,17] but may be less prevalent overall than MCI–multiple domains.[18] The utility of MCI as a diagnostic category, particularly amnestic MCI, is that it has been used operationally to define a "predementia" state amenable to therapeutic interventions whose efficacy can be defined by the conversion rate of MCI to dementia.[19]

Longitudinal studies of patients with MCI have shown a conversion rate to dementia of roughly 10% to 15% per year,[11,12,20,21] although conversion rates vary considerably among studies, in part due to different operational definitions of MCI. After 5 years, about half of all patients with MCI will meet the criteria for dementia, particularly AD, and after a 10-year period, most will have AD or another dementia syndrome. At autopsy, approximately 80% of patients originally diagnosed with MCI prove to have AD.[21] Other histopathologic findings were consistent with vascular dementia, frontotemporal dementia, normal aging, and a variety of less common diseases. In most cases, therefore, MCI can be regarded as an early clinical stage of AD.

Although MCI has gained widespread acceptance, challenges remain, including but not limited to the absence of a uniform quantitative or systematic definition of functional impairment. The Clinical Dementia Rating Scale[22] has been used in research studies and has proven to be a valuable instrument for the definition of functional impairment. It is too time-consuming, however, for practical clinical application. Because of the relatively recent definition of MCI subtypes, their incidence, prevalence, neuropathologic correlates, and rates of conversion to Alzheimer's dementia continue to be clarified.

ALZHEIMER'S DISEASE AND ITS RELATIONSHIP TO OTHER DEMENTIAS

Dementing illnesses tend to produce characteristic profiles of cognitive symptoms and signs, although there is considerable variability among patients within any nosologic category. Recognizing diagnostically significant profiles is nonetheless critical for defining specific degenerative syndromes. A patient has AD first and foremost because he or she has the clinical appearance of AD. AD is not simply a diagnosis of exclusion, even if most of the supporting evidence is exclusionary. This is a simple but important concept when considering alternatives, and potentially reversible diagnoses. Uncommon, but reversible diseases (such as nonvasculitic autoimmune inflammatory meningoencephalitis[23]) do not generally reproduce the specific pattern of cognitive deficits that define AD, but that can only be appreciated and recognized if one knows what AD looks like. When a patient's cognitive profile fails to fall into a recognizable degenerative category, particular care should be taken to exclude a potentially reversible cause.

Alzheimer's disease is a pathologically defined disease process that typically results in a characteristic pattern of cognitive deficits that may be termed *Alzheimer's dementia*. Alzheimer's dementia is characterized by prominent memory loss, anomia, constructional apraxia, anosognosia, and variable degrees of personality change in which patients can become mistrustful and aggressive, or frankly delusional and belligerent.[24] Alzheimer's disease does not always produce this pattern, however. Visual variant AD, or posterior cortical atrophy, is a syndrome in which patients develop progressive visual impairment related to atypically early and severe degenerative involvement of posterior visual cortices.[25] Other focal variants of AD are less common but include progressive aphasia (typically fluent aphasia), progressive

Table 1. NINCDS-ADRDA Criteria for Probable, Possible, and Definite Alzheimer's Disease (AD)[a]

Probable AD
Dementia established by clinical examination
Dementia confirmed with cognitive testing
Deficits in 2 or more domains of cognition
Progressive decline of memory and other cognitive functions
Preserved consciousness
Onset between ages 40 and 90 years
Absence of systemic or other brain disease that account for symptoms
Possible AD
Atypical onset, presentation, or clinical course of dementia
Another illness capable of producing dementia is present but is not considered to be the primary cause
Definite AD
Clinical criteria for probable AD
Tissue diagnosis by autopsy or biopsy

[a]Reprinted with permission from McKhann et al.[33]
Abbreviation: NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association.

Table 2. DSM-IV-TR Criteria for Dementia of the Alzheimer's Type[a]

Insidious onset with progressive decline of cognitive function resulting in impairment of social or occupational functioning from a previously higher level
Impairment of recent memory
Disturbance in at least 1 of the following cognitive domains:
Aphasia
Apraxia
Agnosia
Executive functioning (planning, organizing, sequencing, abstracting)
Cognitive deficits are not due to other neurologic, psychiatric, toxic, metabolic, or systemic diseases
Cognitive deficits do not occur solely in the setting of a delirium

[a]Reprinted with permission from American Psychiatric Association.[34]

apraxia, and progressive frontotemporal dementia.[26–32] Anecdotally, the more posterior variants of AD, such as visual variant and apraxic forms, may be less prone to behavioral difficulties than the typical and more anterior (aphasic and frontotemporal) forms.

Commonly used criteria for the diagnosis of AD were described by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) joint task force in 1984[33] and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR).[34] NINCDS-ADRDA diagnostic criteria for probable, possible, and definite AD are shown in Table 1. Criteria for probable AD include dementia with cognitive deficits in at least 2 cognitive domains including progressive memory loss, normal level of consciousness, onset between ages 40 and 90 years, and the absence of another plausible medical explanation. If there is another illness that might be contributing to the clinical picture but is not felt to be the primary cause of dementia or if the picture is dominated by a progressive focal cognitive deficit (for example, progressive aphasia), then the term *possible AD* is used. The diagnosis of definite AD requires the neuropathologic diagnosis of AD (typically at autopsy, but sometimes from a brain tissue biopsy).

As shown in Table 2, DSM-IV-TR criteria for dementia of the Alzheimer's type include a gradual and progressive decline in cognitive function resulting in impairment of social or occupational function and impairments in recent memory and at least 1 other cognitive domain (aphasia, apraxia, agnosia, or executive functioning) that are not due to other psychiatric or nonpsychiatric medical problems. (Since neuropathologic confirmation is not required, DSM-IV-TR criteria for dementia of the Alzheimer's type most closely resembles NINCDS-ADRDA criteria for probable AD).

RELATED DISORDERS

The differential diagnosis of AD is extensive, but there are 3 disorders in particular in which there is extensive overlap pathologically and/or clinically that blur into the nosologic boundary of AD.

Dementia With Lewy Bodies

Patients with dementia, parkinsonism, visual hallucinations, and rapid eye movement (REM) sleep behavior disorder (characterized by movements of the body or limbs in association with dreaming and REM sleep) often have dementia with Lewy bodies.[27,31,32] Lewy bodies are intracytoplasmic inclusions composed of α-synuclein, and are a defining feature of Parkinson's disease.[35] In patients with Parkinson's disease, the Lewy bodies are concentrated in the brain stem catecholaminergic nuclei, principally the substantia nigra, locus ceruleus, and dorsal motor nucleus of the vagus nerve. In dementia with Lewy bodies, Lewy bodies are found in these same regions but are also spread throughout the amygdala, entorhinal cortex, and neocortex.[36]

The characteristic cognitive profile of dementia in patients with dementia with Lewy bodies includes impaired learning and memory, psychomotor slowing, constructional apraxia, and more profound visual-spatial impairment than in similarly staged patients with AD.[37] The separation is not complete, however, as more than three quarters of all patients with dementia with Lewy bodies have concomitant neuropathologic features of AD.[38–41]

Distinguishing the relative contributions to dementia of α-synuclein–based and AD-based pathology in patients with dementia with Lewy bodies is not clear cut. Most patients with clinically diagnosed dementia with Lewy bodies have AD pathology in addition to neocortical Lewy bodies at autopsy,[38–41] but among patients with neuropathologically diagnosed AD, neocortical Lewy bodies

can still be found in 25% to 60% of brains.[42–44] Importantly, patients with dementia with Lewy bodies may have greater extrapyramidal sensitivity to antipsychotic medications than those with pure AD.[31]

Vascular Dementia

Multiple proposed diagnostic criteria exist for the diagnosis of vascular dementia, with poor agreement among them.[34,45–47] Vascular mechanisms of cognitive loss include the direct consequences of brain infarctions, hemorrhages, and global hypoxia-ischemia. The 2 major subtypes of vascular pathology in patients with vascular dementia are multiple large artery territory infarctions (and/or hemorrhages) and small vessel cerebrovascular disease caused either by arteriolosclerosis or amyloid angiopathy. In the large artery type, clinically evident strokes occur with consequent accrual of deficits. This is not a slowly progressive disease but one of defined events. An ongoing controversy, however, is whether AD develops at an accelerated rate following (and, by implication, as a result of) cerebral infarction (or hemorrhage).[48,49] Recent investigations have also established that risk factors for atherosclerotic vascular disease are also risk factors for AD and that there is a statistically significant association between AD and atherosclerosis of major intracranial arteries.[48,50–52]

Small vessel cerebrovascular disease, however, is more subtle, often with no defined events (or with few as a minor component). Patients have a more subcortical pattern of dementia with psychomotor slowing, a poor learning curve, and relative preservation of naming and other language skills. Within this context, a mixed pathologic picture with both vascular disease and AD is common, whether the underlying vasculopathy is atherosclerotic[53–55] or amyloid based.[56–59]

Hippocampal Sclerosis Dementia

In a subset of elderly individuals with dementia,[60] hippocampal sclerosis is the only remarkable autopsy finding. The frequency of hippocampal sclerosis in autopsy series of elderly demented persons has been reported to be as low as 0.4% and as high as 26%. During life, these cases are usually diagnosed as AD since they typically present with memory loss that progresses to dementia. The cause of hippocampal sclerosis associated with dementia (HSD) is unknown; there is rarely a history of seizures or of a global cerebral hypoxic-ischemic event, which are associated with hippocampal sclerosis in other settings. It has been suggested that HSD is due to occult hypoxic-ischemic episodes or limbic encephalitis. A large subset of HSD cases have a distinctive cerebral neuronoglial tauopathy,[61] which suggests that this condition should be classified as neurodegenerative. To date, antemortem distinction of HSD from AD has not been reliable, even with extensive neuropsychologic test batteries.[61]

DIAGNOSTIC EVALUATION

History and Physical Examination

AD is typically gradual in onset. The most common initial symptom is memory loss, and this remains a prominent deficit throughout the clinical course. In addition to memory loss, other cognitive deficits include anomia, constructional apraxia, and often anosognosia (i.e., unawareness of one's impairment). As the disease progresses, there is greater overlap of symptoms and deficits with other dementing illnesses so that distinguishing AD from other forms of dementia is more reliable in mild to moderate–stage disease. It is also critical to place the patient's symptoms within the context of his or her medical background. Medication use, concurrent systemic illness, prior brain-related illness, and psychiatric disease can affect the clinical presentation, diagnosis, treatment options, and prognosis. Family history of dementia in a parent or other relative is common. Pertinent concerns in the social history include driving habits, whether the patient lives alone or with a potential caregiver, recreational habits (use of tobacco or alcohol, possession of weapons at home), and educational and occupational history.

There are no telltale signs on physical examination in typical cases, but in atypical cases, there may be focal signs reflecting the altered topography of the disease such as aphasia, apraxia, or cortical visual impairment. Mental status testing is critical. Most types of mental status tests include questions related to orientation, attention, learning, memory, language, and constructional praxis as illustrated by the Folstein Mini-Mental State Examination.[62]

Neuropsychological Assessment

To help define the pattern and severity of cognitive loss, neuropsychological testing can supplement the clinical cognitive assessment. The 3 main questions that neuropsychological assessment can answer are:

1. Is there a problem? This is relevant in mild cases, especially when there is disagreement between the patient and others.
2. What is the pattern of difficulty? This is the "positive" evidence of a specific nosologic entity so that the diagnosis of AD is not simply a diagnosis of exclusion.
3. How severe is the problem? Lifestyle changes such as cessation of driving and assisted living are based on degree of functional impairment that, in turn, correlates with degree of intellectual impairment as disclosed by neuropsychological testing.

Therefore, while useful in almost any patient with dementia, neuropsychological testing can be particularly helpful in assessing mild cases, medicolegally contested

cases, and cases where major lifestyle changes will likely be imposed.

Brain Imaging

Structural brain imaging with magnetic resonance imaging (MRI) or computed tomography (CT) is essential to assess for relevant structural pathology such as brain tumors, vascular lesions, subdural hematomas, hydrocephalus, and other problems. In patients with AD, MRI and CT typically reveal nonspecific, mild to moderate atrophy that may be most pronounced in the most symptomatic regions, especially the medial temporal lobe. Cerebral white matter hyperintensities are a frequent finding in the nondemented elderly and are approximately twice as common in AD subjects. (Postmortem studies have shown that, compared with nondemented elderly cases, AD cerebral white matter has significantly less protein, cholesterol, and cell density.[50]) While radiologists often refer to these white matter abnormalities as *small vessel ischemic changes*, their etiology is presently unproven as they may also represent secondary degeneration of the white matter after primary cortical AD pathology. Quantitative volumetric MRI can track progressive hippocampal atrophy that correlates with symptomatic disease progression but is not usually performed in routine clinical settings.

Although structural neuroimaging plays an important role in excluding alternative causes of dementia, some investigators have suggested that fluorodeoxyglucose (FDG) positron emission tomography (PET) may be helpful in distinguishing AD from frontotemporal dementia and other less common forms of dementia, particularly in the earliest clinical stages of the disorder or when patients exhibit atypical clinical features, when the diagnosis may be less certain. Patients with AD have characteristic and progressive patterns of decline in regional glucose metabolism, beginning in posterior locations (the precuneus and posterior cingulate, posterior parietal, and temporal cortex), and subsequently affecting prefrontal cortex and the whole brain.[63] 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 neuropathologic assessments an average of 3 years later, FDG PET readings were associated with about 93% sensitivity and 75% sensitivity in predicting subsequent clinical decline and the neuropathologic diagnosis of AD.[63] Based on these and other findings, the United States Center for Medicare and Medicaid determined that FDG PET is reasonable and necessary in patients with documented cognitive decline and a recently established diagnosis of dementia who met clinical criteria for both AD and frontotemporal dementia, who had 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; available at: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=104). The Center also found that the evidence is not yet adequate to conclude that FDG PET is useful in the evaluation of patients with mild cognitive impairment or other patients with dementia and expressed interest in supporting studies that would further evaluate the imaging technique's ability to predict and improve clinical outcomes.

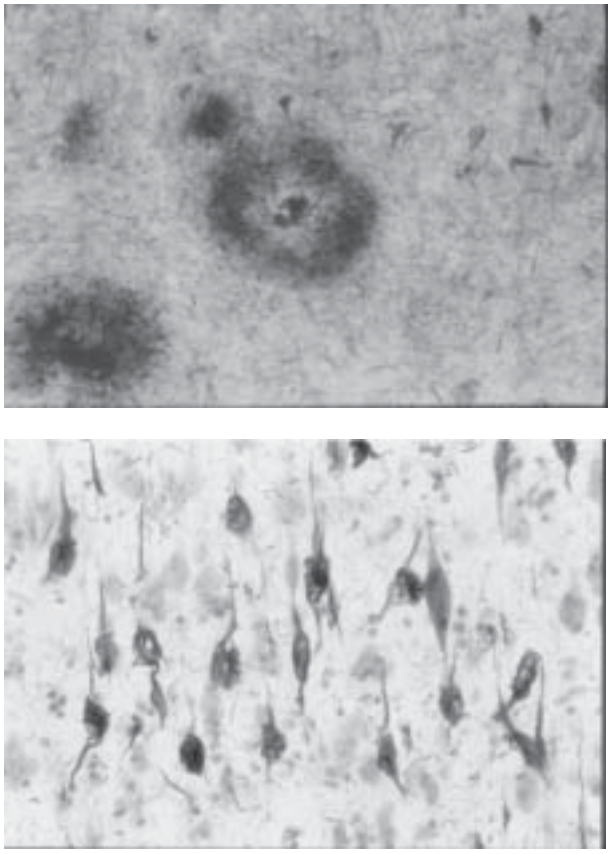
Several small studies[64,65] have raised the possibility that FDG PET may help predict rates of subsequent cognitive decline and conversion to dementia in patients with MCI. Most, but not all,[64] were retrospective in nature, and there was some overlap between the PET measurements or readings of the patients who did and did not subsequently convert to AD. Additional research, like that now being conducted in the National Institute on Aging–sponsored AD Neuroimaging Initiative, is needed to further evaluate this potential indication before it can be recommended in clinical evaluation of MCI.[65]

Recently, investigators have developed promising PET and single-photon emission tomography (SPECT) radiotracer methods for the assessment of fibrillar amyloid deposition, a cardinal feature of AD, in the living human brain. Some of the best developed fibrillar amyloid ligands include the PET tracers "Pittsburgh Compound-B,"[66,67] fluoro-dicyano-dimethylamino-naphthalenyl-propene (FDDNP),[68] and *N*-methylamino-hydroxystilbene (SB-13)[69] and the SPECT tracer iodo-dimethylamino-phenyl-imidazopyridine (IMPY).[69] These and other fibrillar amyloid imaging techniques and their underlying assumptions continue to be developed, tested, and applied. It remains to be shown the extent to which these techniques can be used clinically to predict subsequent clinical decline and the histopathologic diagnosis of AD and to guide patient management.

Laboratory Assessment

There are no widely accepted, highly reliable, commercially available biomarkers for AD; therefore diagnosis rests on clinical recognition as well as exclusion of potentially contributory medical factors. The medical factors evaluated should be appropriate for the patient's medical background. If a patient is generally healthy, those should still include blood tests for thyroid function, vitamin B12 level, complete blood counts, metabolic function (including tests of liver and renal function and glucose, electrolytes, and calcium). Other tests should be considered as appropriate for the patient's medical background. For example, if a patient has a recent history of lung cancer, then a chest x-ray, erythrocyte sedimentation rate, and contrast enhanced brain imaging may be appropriate to assess for possibly active metastatic disease. Before cholinesterase inhibitor therapy is prescribed, a baseline electrocardiogram should be obtained to insure the patient does not have severe conduction abnormalities

Figure 1. Neuropathology of Alzheimer's Disease (top: neuritic amyloid plaques [Campbell-Switzer stain], bottom: neurofibrillary tangles [Gallyas stain])



that might be exacerbated by therapy. These are simply 2 examples, and not a comprehensive list.

Patients with unusually rapid symptomatic progression, myoclonus, depressed level of consciousness, or other forms of presentation that would be atypical for AD might be considered for spinal fluid examination. In patients who undergo spinal fluid examination, tests sensitive to infection, malignancy, and inflammatory diseases should be obtained. More controversial is the use of putative biomarkers for AD including cerebrospinal fluid measurements of certain amyloid β–peptide (Aβ) and tau proteins. Patients with AD have cerebrospinal fluid (CSF) reductions in a form of Aβ (Aβ42) and increases in CSF tau, but there is some overlap between AD and other subject groups.[70] (Other CSF, blood, and urine biomarkers continue to be investigated). Electroencephalography can be considered in patients suspected of having seizures, encephalopathic disorders, or rapidly progressive forms of dementia such as Creutzfeldt-Jakob disease. Again, these examples should not be considered exhaustive, and other tests may be appropriate depending on the specific medical background of a given patient.

NEUROPATHOLOGY OF ALZHEIMER'S DISEASE

A diagnosis of definite AD requires microscopic examination of the cerebral cortex.[33] Cortical biopsy can provide a definitive diagnosis during life but is not routinely performed, so a definitive diagnosis of AD is typically obtained after death. A succession of neuropathologic diagnostic criteria for AD has been established over the past 20 years, with successive refinements. The National Institute on Aging established criteria in 1985 that required specific cortical senile plaque densities.[71] Cortical neurofibrillary tangles were not required for diagnosis, as some cases of AD were known to be "plaque-only."[72] The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) published criteria in 1991[73] that gave diagrammatic semiquantitative standards for assessing plaque density (none, sparse, moderate, or frequent) and specified that only neuritic plaques were relevant for diagnostic purposes (excluding "diffuse" plaques). The diagnosis again was defined solely on the basis of cortical plaque density, without a requirement for the presence of cortical neurofibrillary tangles.

In 1997, a committee formed under the auspices of the National Institute on Aging and the Reagan Institute published new diagnostic criteria that included cortical densities of both neuritic plaques and neurofibrillary tangles.[74] These criteria recognized that dementia in the elderly can be due to more than one cause. Therefore, rather than emphasize an absolute diagnosis of AD, instead it emphasized the probability that dementia was due to AD. High cortical densities of both plaques and tangles (Figure 1) are designated as "high likelihood that dementia is due to Alzheimer's disease," with lower densities being assigned "intermediate" or "low" likelihoods. An unresolved issue with all diagnostic criteria for AD is the significance of plaques and tangles in nondemented elderly persons. Current practice restricts the diagnosis of AD to those diagnosed with dementia during life, but clearly this may result in underestimating the number of elderly with the disease who die during a preclinical stage.

PATHOGENESIS OF ALZHEIMER'S DISEASE

The cause of AD is inferred to relate to the signature microscopic lesions of the disease, which are the senile plaque and the neurofibrillary tangle,[75] and ultimately to the loss of synapses and neurons. The accumulated evidence suggests that plaques occur prior to tangles in neocortical regions and that the latter are formed mainly as a neuronal reaction to plaques (although the earliest neurofibrillary changes in transentorhinal and entorhinal cortex may precede other neuropathology). The plaques themselves are formed from deposition of the amyloid β-peptide (Aβ) that deposits in an aggregated fibrillar form of amyloid. The "amyloid hypothesis" posits that Aβ

aggregation is the primary event leading to AD[76–78] that secondarily causes all of the other relevant pathologic changes in the disease, including neurofibrillary tangle formation, loss of synapses, neuronal death, and dementia. (Increasing evidence suggests that soluble Aβ oligomers may be more damaging to neurons than the nonsoluble plaques, themselves.) Strong support for the amyloid hypothesis comes from known autosomal-dominant mutations that lead to early-onset familial AD. These mutations are found on genes for the amyloid precursor protein (*APP*) on chromosome 21, presenilin 1 (*PS1*) on chromosome 14, and presenilin 2 (*PS2*) on chromosome 1, each of which leads to an overabundance of Aβ. The existence of other cerebral amyloidoses that cause plaques, tangles, and dementia supports the viewpoint that AD is one form of cerebral amyloidosis.[79,80] Animal models of AD have also supported the amyloid hypothesis, as insertion of human APP (the larger protein that contains abeta within it) gene mutations into transgenic mice results in abeta amyloid plaques. Tangles do not form in these mice, however, unless mutant tau protein genes are also inserted, leaving these models short of complete recapitulation of the human disease.[81] This has led some to argue that these transgenic mouse models are simply a form of cerebral amyloidosis, but not AD.

Aβ fragments are generated from the cleavage of the amyloid precursor protein (a transmembrane protein found in all cells) by 3 types of proteases, which are designated α-, β-, and γ-secretases. As cleavage by α-secretase destroys the Aβ sequence, it is generally thought that the α-secretase pathway mitigates amyloid formation, although this has not been demonstrated unequivocally.[82] The β-secretase cleaves APP first to generate a 99-amino acid membrane–associated fragment (CT99) containing the N-terminus of Aβ.[83] The γ-secretase then cleaves within the transmembrane region of CT99 to generate the C-termini of Aβ.[83] The production of Aβ is, therefore, dependent on the activities of both β- and γ-secretase. Evidence indicates that accumulation of Aβ in the brain is an important step in the pathogenesis of AD,[84] and industry and academic researchers have developed a portfolio of promising amyloid-modifying treatments—including but not limited to inhibitors of β- and γ-secretase, antiaggregation therapies, and active and passive Aβ immunization therapies, which have begun to be studied in human clinical trials.

An alternative theory suggests that phosphorylated forms of the microtubule-associated protein tau, a constituent of neurofibrillary tangles, have a primary role in AD pathogenesis. Support for this theory stems from observations that neuronal microtubules are decreased in AD, and axonal terminals are dependent on them for axoplasmic flow.[85] Studies have shown that high neurofibrillary tangle densities in the entorhinal and hippocampal neurons strongly correlate with memory impairment in aging, and immense neurofibrillary tangle concentration within adjacent components of the medial and inferior aspects of the temporal cortex is associated with clinically overt AD, whereas there is little correlation between amount of neuritic plaque and dementia severity.[86] While there are a large number of strategies now being developed to modify amyloid pathology, there are a smaller number of strategies being considered for the modification of tau pathology.[87] Interestingly, 2 mood stabilizing agents, valproate and lithium, have been shown to inhibit glycogen synthase kinase 3β (GSK-3β), a kinase that plays an important role in tau phosphorylation,[88,89] and are the foci of preliminary studies in the treatment of AD. Finally, there are other, less widely held theories for the pathogenesis of AD.

Among the various pathologic signatures, synaptic loss has correlated most closely with clinical measures of dementia severity.[90] Amyloid deposition begins early in the course of the disease but correlates poorly with dementia severity. Neurofibrillary tangle formation correlates well with specific deficits such as memory loss.[91]

GENETICS OF ALZHEIMER'S DISEASE

Elucidation of genetic risk factors for AD has fostered a paradigm shift in our understanding of the genetic basis of disease expression. Two unexpected themes have emerged. First, a single phenotype may reflect genetic mutations of different genes on different chromosomes, disproving the traditional view of 1 gene–1 phenotype. Second, many sporadic cases of AD with no family history of AD are nonetheless genetically determined.

Regarding the multiple gene, single phenotype principle, early-onset familial AD strikes patients when they are young, ranging from mid-thirties to mid-fifties typically. To date, more than 100 mutations of 3 genes have been identified that may cause early-onset familial AD, and all are inherited in an autosomal-dominant pattern. The largest number of mutations is located on the *PS1* gene and is thought to account for the majority of autosomal-dominant kindreds[92]; *PS1* mutations are currently the only autosomal-dominant mutations for which there is a commercially available genetic test. A smaller number of mutations have been localized to the *APP* gene on chromosome 21[93] and to the *PS2* gene on chromosome 1.[94] All result in elevated Aβ levels, underscoring the pathogenetic importance of Aβ in the evolution of AD.[95]

The genetic risk factor that accounts for more cases of AD than any other, however, is the apolipoprotein E (*APOE*) e4 allele located on chromosome 19. *APOE e4* is associated with late-onset familial and "sporadic" AD, but not autosomal-dominant early-onset familial AD.[96,97] *APOE e4* is a prevalent risk factor for AD. Though

prevalence varies worldwide, in North America it is approximately 20%.[98–100]

APOE genotype also appears to influence the age at onset of AD but does not appear to strongly influence the rate of cognitive decline in most patients.[101–105] For instance, each additional copy of the *APOE e4* gene in a person's genotype is associated with a slightly younger median age at dementia onset. However, *APOE e4* homozygotes with AD may have a faster rate of decline than more common *APOE* subgroups,[106] and several studies have suggested that *APOE* genotype may influence the rate of cognitive decline in nondemented individuals.[107–111]

In addition to enhancing risk for AD, the e4 isoform of *APOE* also correlates with poor neurologic outcome following head trauma[112–114] and intracerebral hemorrhage.[115–117] Although it is not known how *APOE* exerts these effects, possible adverse functional consequences of the e4 isoform compared to the e3 and e2 isoforms include (1) enhanced rate of cerebral amyloid deposition, (2) reduced protection against oxidative injury, (3) reduced efficiency of synaptic and neuronal repair, (4) reduced neurotrophic properties possibly related to reduced tau binding causing microtubule destabilization and consequently reduced neurite outgrowth,[118] and (5) e4 isoform specific intraneuronal proteolysis induced carboxyl fragment toxicity.[119–121] These effects are not mutually exclusive and all may be operational to varying degrees. Several of these possibilities, however, suggest that *APOE* genotype, apart from its role in senescence and injury, could influence neural development.[122–124]

The search is on for the discovery of additional susceptibility genes for late-onset AD. For instance, some studies have raised the possibility that additional genetic loci, identified more recently on chromosomes 10[125] and 12,[126] may account for late-onset AD. Finally, weaker genetic risk factors in cholesterol and glucose metabolic pathways may further influence the cumulative genetic risk for late-onset or "sporadic" AD.[127–129]

As recently noted in this journal,[130] high-density single nucleotide polymorphism genetic arrays may help to identify many of the remaining susceptibility genes that account for about 70% of the risk of AD. The recently developed AlzGene database aims to provide an unbiased, publicly available, and regularly updated review of AD genetic linkage and association studies (available at: http://www.alzforum.org/res/com/gen/alzgene/).[130]

Genetic Testing

Although not part of the routine care of patients with AD, genetic information is becoming more commonplace in medicine and in the mind of the lay public. Relatives of patients frequently ask about the likelihood that AD can be inherited and even about the option of genetic testing of the patient and family members.

The genetics of AD are complex, but the main distinction to be drawn in deciding whether or not to pursue genetic testing is whether the testing will have any beneficial clinical effects. In the case of testing for the *PS1* genetic mutation in patients with early-onset familial AD, genetic testing should be considered, particularly because it can be used to test presymptomatic at-risk family members who may alter important life decisions on the basis of the results. Counseling of possible outcomes needs to be started before any testing is pursued in order to prepare the individual for the possible results and their implications.

Deciding whether to perform *APOE* testing is more problematic. Should patients with AD be tested? Because *APOE e4* is so prevalent, there are many *APOE e4* carriers with brain-related illnesses other than AD. *APOE* status does not affect the therapeutic alternatives for a patient with AD. Because the negative predictive value of *APOE* is poor, it is not very helpful in routine clinical settings where the emphasis is on finding alternative and potentially reversible causes of dementia. "Negative" *APOE e4* test results do not preclude a diagnosis of AD. On the other hand, *APOE* testing does increase the positive predictive value of diagnosis.[131]

Consensus work groups have discouraged the use of *APOE* genotyping to predict the risk of AD in healthy persons, whether or not they have a family history of AD, because (1) *APOE* testing does not predict with sufficient certainty whether or when a person might develop the clinical features of AD, (2) the information could lead to false alarm and the potential for psychological harm or false reassurance, (3) there is the risk of inadvertent exposure to information by the relatives of a patient with the *APOE e4* homozygote, and (4) no established treatment exists that hinges on information about a person's genetic risk. In the meantime, however, some investigators have challenged the consensus view that *APOE* testing should not be recommended to help predict the risk of AD in interested individuals, and the National Institutes of Health–sponsored "Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study[132,133] trial is examining the impact of a genetic risk assessment program, including genetic counseling and *APOE* genotype disclosure in adult children of patients with AD.

We and others have been conducting studies of healthy persons with 2 copies, 1 copy, and no copies of the *APOE e4* allele (in which our volunteers have agreed not to receive information about their *APOE* genotype). These studies have begun to characterize the functional imaging, structural imaging, and cognitive changes that precede the onset of symptoms in healthy persons at differential genetic risk for AD.[134–142] They may provide a foundation for testing promising preliminary prevention therapies without having to wait many years to determine whether or when the volunteers develop symptoms.[135]

© COPYRIGHT 2006 PHYSICIANS POSTGRADUATE PRESS, INC.

TREATMENT

The general principles of management are to slow and smooth the expected progression of disease, to maximize the patient's quality of life, and most importantly, to help the family succeed in their role as primary caregivers. The 2 broad categories of management are pharmacotherapy and lifestyle changes.

Pharmacotherapy

Cognitive decline. Two classes of drugs have been approved for use to enhance memory and related intellectual skills in patients with AD: the cholinesterase inhibitors[143–145] and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine.[146] Three cholinesterase inhibitors are currently used for the treatment of mild to moderate AD: donepezil, galantamine, and rivastigmine. Tacrine was the first acetylcholinesterase inhibitor approved by the U.S. Food and Drug Administration (FDA) for AD but is no longer recommended due to its side effect profile including hepatotoxicity. Donepezil[147] is a once-a-day medication. Rivastigmine[148] has also been shown to inhibit butyrocholinesterase, the clinical significance of which remains unclear (and it has a higher incidence of nausea than the other 2 currently used cholinesterase inhibitors). Galantamine[145] also binds to nicotinic receptors, the clinical significance of which remains unclear.

As a class, these agents have demonstrated measurable, though modest, effects on cognition, activities of daily living, and global measures of functioning versus placebo in clinical trials.[149] For the most part, treatment goals focus on delaying worsening of these clinical features, although a minority of patients can actually show temporary partial improvement. There is mounting evidence that these agents can have beneficial effects on behavioral symptoms as well. Although generally well-tolerated, the main adverse effects are gastrointestinal (nausea, vomiting, diarrhea, anorexia, weight loss), and these medications are better tolerated on a full stomach. Insomnia, vivid dreams, and leg cramps have also been reported in a small percent of cases. Bradycardia, usually insignificant, is a side effect that can be dangerous in patients with cardiac conduction deficits, hence supporting the performance of an electrocardiogram prior to treatment.

The choice of which acetylcholinesterase inhibitor is most appropriate for each patient is based on titration schedule, dosing regimens, and side effects. Meta-analyses and treatment guidelines do not suggest important differences in efficacy, but do note differences in the frequency of side effects. For instance, donepezil can be administered once daily and has been suggested to have fewer side effects than rivastigmine.[150,151] Studies are needed to further assess possible long-term benefits such as delayed institutionalization and economic savings in the cost of patient care. Although data regarding how long patients should continue taking an acetylcholinesterase inhibitor are limited,[152,153] a case could be made to treat patients indefinitely in the hope of slightly delaying the cognitive decline that might have occurred after stopping treatment, unless side effects or other individualized issues arise.

At this time, the FDA has approved cholinesterase inhibitors for the treatment of mild to moderate stages of AD and memantine for the moderate to late stages of AD. There may be some benefit to the addition of one medication class following a full therapeutic trial of the other class. More recently, the issue of cost-benefit has arisen and is controversial, with some claiming therapy reduces long-term costs and others claiming it simply adds to long-term costs.[154]

Behavioral problems. There are 3 categories of behavioral problems that are commonly encountered in patients with AD and related forms of dementia.

Psychosis. Psychosis includes hallucinations (typically, but not exclusively, visual), paranoid delusions, and agitation (particularly sundowning). There are no agents that have received FDA approval for the specific treatment of agitated, delirious, psychotic elderly patients with dementia. In the absence of definitive clinical trials, anecdotal experience and meta-analysis[155] suggest that atypical antipsychotic agents may be the preferred agents, especially in patients with parkinsonism, because they can be effective and because they are less likely to cause or exacerbate extrapyramidal syndromes. They currently lack FDA approval for such an indication; therefore, clinical judgment is essential. Further, the FDA recently required a black box warning label on the use of atypical antipsychotics in the treatment of elderly patients with dementia because of unpublished data suggesting an increased risk of mortality (http://www.fda.gov/cder/drug/advisory/antipsychotics.htm). Alternate recommendations were not given, and in the absence of a clear alternative, many clinicians continue to feel that these medications remain an important therapeutic option for managing severe behavioral problems. Older agents (the "typical" antipsychotic drugs such as haloperidol) are effective but have a high likelihood of causing or exacerbating parkinsonism and a much higher risk of tardive dyskinesia if used chronically. A more recent analysis suggested that mortality associated with neuroleptic use in the older dementia population is more frequent in those treated with conventional neuroleptics compared with the newer atypical neuroleptics.[156] Therefore, use of atypical neuroleptics can be justified, provided that the patient's family and other physicians involved in a patient's care feel the benefits outweigh the risks. As with all psychoactive medications, care must be used to minimize the dose and duration of use.

Depression. Depression is common in patients with AD. Drugs with anticholinergic properties, such as the

tricyclic antidepressants, should be avoided because of the risk of exacerbating confusion. Selective serotonin reuptake inhibitors (SSRIs) are preferred[157] and sometimes can also help to ease agitation. However, SSRIs may occasionally precipitate REM sleep behavior disorder.[158] In patients with depression who are also having trouble sleeping, some clinicians have advocated the use of a sedating antidepressant, such as trazodone, at bedtime, though randomized controlled trials are lacking and side effects such as orthostatic hypotension should be considered.

Anxiety. Some patients will not let their caregiver out of their sight, and this can quickly wear down the caregiver. If other treatments are not effective, a low dose atypical antipsychotic medication as described above might be considered.[159,160]

Sleep disorders. Of the many possible sleep disorders that can affect patients with dementia, the following 4 are perhaps the most frequently troublesome.

Simple insomnia. In simple insomnia, the patient will not fall asleep or else gets up very early and will not go back to sleep. A short-acting sedative-hypnotic such as zolpidem or zaleplon is often effective and may be given either at bedtime or when the patient wakens in the night.[160,161] Antihistamines are not recommended because of their lack of established efficacy and side effect profile.

REM sleep behavior disorder. In REM sleep behavior disorder, patients have dream enactment behavior associated with a loss of muscle atonia on polysomnographic electromyogram recordings due to involvement of cholinergic brainstem nuclei within the context of a synucleinopathy, particularly dementia with Lewy bodies.[27] This can be difficult to treat, but some clinicians have advocated the use of low-dose clonazepam, while monitoring patients carefully for any benzodiazepine-related exacerbation in cognitive impairment or ataxia over the next few weeks.

Obstructive sleep apnea. Obstructive sleep apnea (OSA) should be suspected in any overweight patient complaining of daytime somnolence. In patients with OSA and mild cognitive difficulties, treating underlying OSA can sometimes improve their cognitive syndrome. OSA is not a cause of dementia but can be a cause of mild cognitive complaints that may be mistaken for early stage AD. It is also found more commonly in persons with APOE e4,[162,163] which is commonly found in patients with AD. A simple screening test can be overnight oximetry, but if truly suspected, a formal sleep study and continuous positive airway pressure trial should be obtained.

Nocturia. Though not a primary sleep disorder, nocturia is a common reason some patients with dementia are up at night and tired during the day. Treatment options for incontinence are described later.

Associated problems. Some associated problems commonly occur in the dementia population. While some of these problems may be addressed by another physician, it is helpful for the dementia-treating physician to be aware of the problem and management options.

Parkinsonism. Mild parkinsonism can be an important diagnostic sign of dementia with Lewy bodies and related disorders. Intervention with dopaminergic medications can potentially create or worsen psychotic symptoms, particularly visual hallucinations in vulnerable patients. Treatment should therefore be reserved for those with clinically significant parkinsonism, especially if balance becomes impaired so that falls become a threat. An arguably related condition, normal pressure hydrocephalus (NPH), has gained recognition by the clinical triad of dementia, gait disorder, and incontinence. This triad is not unique to NPH, and occurs eventually in many patients with dementia. Nonetheless NPH remains an important diagnostic consideration since it can sometimes be reversed. NPH usually begins as a predominant gait disorder that is unresponsive to antiparkinsonian medications. When correctly diagnosed, it may be treated surgically with ventriculoperitoneal shunting.

Urinary incontinence. Two of the more common causes of urinary frequency and incontinence in patients with dementia are flaccid distended bladders that cause overflow incontinence and spastic bladders. They are easily distinguished by checking a urinary postvoid residual. The former is treated with intermittent catheterization. The latter can usually be managed with peripherally acting anticholinergic agents such as oxybutynin and tolterodine. These agents risk exacerbating confusion, and so care must be taken, but if started at low doses and titrated gradually can often be used safely and effectively.

Other physical deficits. Other physical deficits may be disease specific, such as apraxia in patients with corticobasal ganglionic degeneration, dysphagia in patients with amyotrophic lateral sclerosis-dementia complex, and cortical visual syndromes in patients with visual variant AD (or "posterior cortical atrophy"). These are not generally responsive to medications, but appropriate physical/occupational therapy and safety interventions should be addressed.

Abrupt Decline

Over the protracted course of AD, many patients have times when they suddenly become much more confused, with slurred speech, somnolence, agitation, tremulousness, unsteadiness, falls, and worsened incontinence. Often, this is due to a superimposed illness, typically an infection (urinary tract or pneumonia most commonly), a medication error, an injury of some type, or some other cause that must be sought with a thorough evaluation.

Lifestyle Changes

Driving. One of the more difficult lifestyle changes for patients with dementia to accept is not driving. The Clinical Dementia Rating (CDR)[22] is a widely utilized clinical

tool for grading the relative severity of dementia with scores that range from 0 (no impairment) to 3 (severe impairment). Patients with MCI typically have a CDR score of 0.5 and comprise an identifiable subgroup of patients that can be distinguished from those with significant functional impairment or with impairment of multiple cognitive domains that include but are not confined to memory.[13-15] According to the Practice Parameter of the Quality Standards Subcommittee of the American Academy of Neurology, patients with mild cognitive impairment and a CDR score of 0.5 should be cautioned. While there is typically no absolute restriction on driving in the absence of overt driving impairment reported either by the patient or a reliable observer, physicians should be aware of reporting requirements in their area. For instance, California requires physicians to report the diagnosis of dementia to the Department of Motor Vehicles. However, the practice parameter advises they be reassessed periodically (every 6 months) until they have declined to a CDR score of 1.0 (or the equivalent), and at that point, the standard changes to no driving. Therefore, according to the practice parameter, a patient with mild AD and a CDR score of 1.0 is to be advised that he or she is not to drive.[164]

There are many simple reasons why patients with dementia may not be able to drive. Patients with visual variant AD have disabling visual impairment.[165] Patients with progressive apraxia related to corticobasal ganglionic degeneration have severe motor impairment, and some additionally have visual impairment. Patients with primary progressive aphasia (PPA) sometimes are capable of driving, but due to the speech disturbance occurring within the context of a dementing degenerative brain disease, they would be ill equipped to explain themselves in the event of a mishap and legally would be difficult to defend if challenged. (Hence, it is probably best that they not drive). Impaired attention, inability to "multitask," and other cognitive disturbances in addition to memory loss all impair driving skills as shown on actual road tests[166–169] as well as on driving simulation tests[170–173] resulting in a 2- to 8-fold increase in rate of collisions in patients with AD who continue driving.[164]

Simply telling a patient with dementia not to drive often is not sufficient, and many continue to drive even after they develop evident driving impairment despite admonitions not to drive.[174,175] Patients may take a driving test, and when they do, 40% to 60% fail,[176,177] but losing their license only makes it illegal for them to drive. The most effective way to stop a patient from driving is to remove their access to car keys or the car itself. This is not always easy to accomplish and has caused some patients to become belligerent, so care must be used in managing this very difficult but important issue.

Other safety issues. Caregivers should be advised to address home safety. The home environment should remain familiar and uncluttered, with ample lighting, especially at night, to prevent falls and injuries. Other examples of home modifications include installing locks on cabinets, cupboards, and ovens and removing knobs on the stove. The treating physician should ask about access to firearms in the home and suggest their safe storage or removal. Families should be instructed to keep poisonous or harmful substances and sharp objects out of reach. Caregivers should be encouraged to register relevant patients in the Alzheimer's Association's Safe Return Program, an identification program for dementia patients who have a tendency to wander.

There has been relatively little written about proper handling of weapons in dementia households,[178,179] save that the issue exists and would seem to pose a serious risk. One study found that gun ownership was prevalent in 60% of "dementia households" and that the guns were known to be deliberately kept in an unloaded state in only 17% of those households with guns.[179] Common sense would argue that weapons should be addressed at least as consistently as driving, and perhaps with even greater sensitivity. Secured storage sites, unloaded weapons, and similar measures should be considered.

Assisted living and skilled nursing facilities. Patients with dementia require assistance with activities of daily living, behavioral supervision, assistance with medication use, and essentially assistance with every aspect of daily life. This is a 24-hour job, and one that is taxing on a caregiver so that caregiver burnout and depression is a common occurrence.[180] As long as a caregiver or family member is able to cope with a patient's needs, there are few absolute reasons that mandate placement of a patient into a supervised assisted living or nursing home setting. As might be anticipated, predictors of such placement include increasing severity of dementia, increased burden of need, and reduced availability of caregivers.[181,182] Someone living alone is at very high risk and so is most likely to require placement, whereas a patient with multiple family members who are available to help with nighttime as well as daytime behaviors is least likely to require placement. Some studies have shown that treatment with cholinesterase inhibitors delays nursing home placement by between 1 and 2 years.[183,184]

Other important lifestyle issues include living wills, power of attorney, and legal guardianship. These provide for the disposition of care in the absence of current patient competency, the protection and management of a patient's estate, and the ability of a trusted caregiver to become the legal guardian of the patient.

The care provider. Patients with dementia usually have at least 1 caregiver, and the clinician must recognize his or her vital role in management. Physicians should routinely educate the caregiver about the disease, as well as assess his or her own emotional well-being. Caregivers of relatives are at high risk of depression, far in excess of age-matched comparison subjects.[185] Long-term social

Table 3. Some Investigational Approaches to the Treatment of Alzheimer's Disease

Amyloid-modifying medications
β-Secretase inhibitors
γ-Secretase inhibitors
Antiaggregation therapies
Active and passive amyloid-immunization therapies
Tau-phosphorylation inhibitors
Glycogen synthase kinase inhibitors (eg, lithium, valproate)
Antioxidants
Anti-inflammatory agents
Hormonal therapies
Other neuroprotective agents
Neurotrophic agents
Cholesterol-lowering agents
Insulin-sensitizing agents
Antihypertensive agents
Other interventions

Table 4. Some Suggested but Not Yet Established Prevention Therapies for Alzheimer's Disease

Aerobic exercise
Mental exercise
Foods or dietary supplements
Vitamins A, C, E, B12, B-complex supplements
Folate
Gingko biloba extract
Other flavonoids
Other antioxidants
Omega-3 fatty acids (eg, in fish, nuts, and leafy vegetables)
Curcumin (in curry)
Mediterranean diet
Low caloric intake
Low dietary copper
Moderate amounts of wine or other alcohol
Resveratrol (found in grapes and red wine)
Cholesterol-lowering agents
Antihypertensives
Insulin-sensitizing agents
Anti-inflammatory agents
Hormonal therapies (although conjugated estrogen may increase dementia risk when first administered to older women)

support through counseling and support group participation has been shown to result in a significant and sustained decrease in depressive symptoms in caregivers.[186] Therefore, the treating physician should routinely direct the caregiver to counseling, education, and support groups available through community agencies such as the Alzheimer's Association.

Investigational Treatments

While current AD medications improve symptoms, researchers in industry and academia have developed a growing portfolio of promising disease-slowing and prevention therapies (Table 3). Thus, researchers are avidly seeking strategies to prevent or arrest the disease through several different strategies. Because aggregation of Aβ is thought to have neurotoxic properties, one therapeutic strategy is to block Aβ aggregation. Two Aβ aggregation-blockers are currently being tested. Neurochem Incorporated is currently evaluating glycosaminoglycan mimetics[187] and Prana Incorporated is currently assessing iodochlorhydroxyquin, an antibiotic with zinc chelation properties.[188] Zinc is reported to be crucial for Aβ aggregation.

Anti-amyloid immunotherapy trials through immunization treatments are being studied and have shown to markedly reduce AD pathology in the animal models.[189] An active immunization trial, conducted by Elan Corporation and Wyeth, was ended early due to several cases of meningoencephalitis,[190] but these corporations are currently conducting a trial assessing passive immunization and continue to develop active immunization therapies. The ideal active amyloid immunization therapy would be safe and well tolerated, promote an adequate antibody response in older persons while avoiding a potentially more damaging cellular-mediated immune response, clear amyloid plaques, stop and prevent progression of AD pathology, and stop the progression of, partially reverse, and prevent the onset of cognitive decline.

As outlined by the amyloid hypothesis, cleavage by α-secretase is thought to destroy the Aβ sequence thereby mitigating amyloid aggregation, whereas the β-secretase and the γ-secretase are thought to generate Aβ. Thus, some investigational amyloid-modifying therapeutic agents target the inhibition of the β- and γ-secretases and stimulation of α-secretase. For instance, Eli Lilly is investigating a γ-secretase inhibitor that has been shown to be well tolerated and to decrease plasma Aβ.[191]

As previously noted, other amyloid-modifying and tau-modifying treatments continue to be investigated, and investigational disease-slowing treatments of Alzheimer's disease extend beyond amyloid- and tau-modifying therapeutics. These treatments include, but are not limited to, antioxidants, hormonal therapies, other putative neuroprotective and neurotrophic agents, cholesterol-lowering and insulin-sensitizing treatments, and other cardiovascular treatments.

Prevention

While there are no established primary prevention therapies for Alzheimer's disease, researchers have proposed a number of healthy lifestyle changes, dietary supplements, and medications that are worthy of further investigation (Table 4). Some but not all experimental or observational studies suggest several primary prevention therapies worthy of further investigation, including but not limited to aerobic exercise[192]; mental exercise[193]; foods or dietary supplements containing vitamin A,[194] vitamin C,[195] vitamin E,[195] flavonoids,[196,197] omega-3 fatty acids,[198] vitamin B12,[199] vitamin B-complex supplements,[195] folate,[199] or curcumin[200]; caloric intake[201]; the Mediterranean diet[202] (with high intake of vegetables, legumes, fruits, cereals, unsaturated fatty acids primarily from olive oil, moderately high intake of fish, regular but moderate intake of

ethanol primarily from wine, and low intake of meat, poultry, and dairy products); moderate amounts of ethanol or red wine[203] (which have led some to investigate the amyloid-modifying effects of resveratrol in grapes); cholesterol-lowering agents,[204] antihypertensives,[205] insulin-sensitizing agents,[206] and anti-inflammatory agents[207]; hormonal therapies (e.g., perhaps sooner after menopause than in the Women's Healthy Initiative Memory Study which, in contrast to several earlier observational studies, found that estrogen and progesterone administration led to an increased risk of dementia in women who were at least 65 years of age[208,209]); and those putative AD-slowing treatments that prove to be safe and well tolerated in patients.

Even if a prevention therapy proved to be only modestly helpful, it would provide an enormous impact on our public health system. With our aging population, the identification of an effective primary prevention is an increasingly urgent priority. Unfortunately, it would take thousands of healthy volunteers and many years to determine whether or when healthy persons in a randomized clinical trial of a putative prevention therapy develop symptoms. Our ability to detect and track some of the brain imaging changes observed in patients with AD in cognitively normal late-middle-aged carriers of the *APOE e4* allele may provide a way to accelerate the evaluation of promising prevention studies in randomized clinical trials.[135]

CONCLUSIONS

AD is a disorder that takes a terrible toll on patients and their families. Together, physicians, other professional caregivers, and community stakeholders can help recognize and diagnose the problem, exclude and address other causative or aggravating factors, and help patients and families consider the range of medication and nonmedication options best suited to address their needs.

Because of the rapidly growing number of people in older age groups, the prevalence and societal impact of AD is projected to grow exponentially. It is critically important that industry, researchers, and public policy makers work together to find disease-halting and prevention therapies before the problem becomes financially overwhelming. In the last few years, researchers have made great progress in the scientific understanding, early detection and tracking, and treatment and prevention of AD. They have begun to characterize the cascade of molecular events that lead to the neuropathologic features of AD, providing targets at which to aim investigational treatments. They have discovered genetic and nongenetic risk factors for AD, providing additional targets at which to aim investigational treatments and suitable candidates for the study of promising prevention therapies. They continue to develop the use of brain imaging and other biomarker techniques in the unusually early detection and tracking of AD, providing new opportunities to evaluate the effects of new treatments on disease progression and accelerating the evaluation of the most promising treatments. They have already identified and continue to discover promising disease-slowing and prevention therapies that have just begun to be studied in clinical trials. Indeed, researchers have given us the foundation to hope for the identification of disease-slowing and prevention therapies without losing a generation.

Drug names: clonazepam (Klonopin and others), donepezil (Aricept), galantamine (Razadyne), lithium (Eskalith, Lithobid, and others), memantine (Namenda), oxybutynin (Ditropan), rivastigmine (Exelon), tacrine (Cognex), tolterodine (Detrol), trazodone (Desyrel and others), zaleplon (Sonata), zolpidem (Ambien).

REFERENCES

1. Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119–1122
2. U.S. Congress Office of Technology Assessment. Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease and Other Dementias. Washington, DC: U.S. Government Printing Office; 1987
3. Rice DP, Fox PJ, Max W, et al. The economic burden of Alzheimer's disease care. Health Aff (Millwood) 1993;12:164–176
4. Rice DP, Fillit HM, Max W, et al. Prevalence, costs, and treatment of Alzheimer's disease and related dementia: a managed care perspective. Am J Manag Care 2001;7:809–818
5. Ernst RL, Hay JW. The US economic and social costs of Alzheimer's disease revisited. Am J Public Health 1994;84:1261–1264
6. Beach TG, Sue LI, Scott S, et al. Neurofibrillary tangles are constant in aging human nucleus basalis. Alzheimer's Reports 1998;1:375–380
7. Beach TG, Kuo YM, Spiegel K, et al. The cholinergic deficit coincides with Abeta deposition at the earliest histopathologic stages of Alzheimer disease. J Neuropathol Exp Neurol 2000;59:308–313
8. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 1995;16:271–278
9. Braak H, Braak E. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. Neurobiol Aging 1997;18:S85–S88
10. Nagy Z, Hindley NJ, Braak H, et al. The progression of Alzheimer's disease from limbic regions to the neocortex: clinical, radiological and pathological relationships. Dement Geriatr Cogn Disord 1999;10:115–120
11. Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. JAMA 1995;273:1274–1278
12. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308
13. Petersen RC, Stevens JC, Ganguli M, et al. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–1142
14. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992
15. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–246
16. Busse A, Bischkopf J, Riedel-Heller SG, et al. Subclassifications for mild cognitive impairment: prevalence and predictive validity. Psychol Med 2003;33:1029–1038
17. Rasquin SM, Lodder J, Visser PJ, et al. Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment: a 2-year follow-up study. Dement Geriatr Cogn Disord 2005;19:113–119
18. Lopez OL, Jagust WJ, DeKosky ST, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: pt 1. Arch Neurol 2003;60:1385–1389

19. Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004;61:59–66
20. Ganguli M, Dodge HH, Shen C, et al. Mild cognitive impairment, amnestic type: an epidemiologic study. Neurology 2004;63:115–121
21. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397–405
22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414
23. Caselli RJ, Boeve BF, Scheithauer BW, et al. Nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM): a reversible form of encephalopathy. Neurology 1999;53:1579–1581
24. Katzman R. Diagnosis and management of dementia. In: Katzman R, Rowe JW, eds. Principles of Geriatric Neurology. Philadelphia, Pa: FA Davis; 1992:167–206
25. Tang-Wai DF, Graff-Radford NR, Boeve BF, et al. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. Neurology 2004;63:1168–1174
26. Boeve BF, Maraganore DM, Parisi JE, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology 1999;53: 795–800
27. Boeve BF, Silber MH, Ferman TJ, et al. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001;16:622–630
28. Caselli RJ, Jack CR Jr. Asymmetric cortical degeneration syndromes: a proposed clinical classification. Arch Neurol 1992;49:770–780
29. Caselli RJ, Stelmach GE, Caviness JN, et al. A kinematic study of progressive apraxia with and without dementia. Mov Disord 1999;14: 276–287
30. Johnson JK, Head E, Kim R, et al. Clinical and pathological evidence for a frontal variant of Alzheimer disease. Arch Neurol 1999;56:1233–1239
31. McKeith I, Mintzer J, Aarsland D, et al. Dementia with Lewy bodies. Lancet Neurol 2004;3:19–28
32. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872
33. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944
34. American Psychiatric Association. Desk Reference to the Diagnostic Criteria from DSM-IV. Washington, DC: American Psychiatric Association; 1994:85
35. Goedert M. Alpha-synuclein and neurodegenerative diseases. Nat Rev Neurosci 2001;2:492–501
36. McKeith IG. Clinical Lewy body syndromes. Ann N Y Acad Sci 2000; 920:1–8
37. Ferman TJ, Boeve BF, Smith GE, et al. REM sleep behavior disorder and dementia: cognitive differences when compared with AD. Neurology 1999;52:951–957
38. Dickson DW. Dementia with Lewy bodies: neuropathology. J Geriatr Psychiatry Neurol 2002;15:210–216
39. Hohl U, Tiraboschi P, Hansen LA, et al. Diagnostic accuracy of dementia with Lewy bodies. Arch Neurol 2000;57:347–351
40. Iseki E. Dementia with Lewy bodies: reclassification of pathological subtypes and boundary with Parkinson's disease or Alzheimer's disease. Neuropathology 2004;24:72–78
41. Verghese J, Crystal HA, Dickson DW, et al. Validity of clinical criteria for the diagnosis of dementia with Lewy bodies. Neurology 1999;53: 1974–1982
42. Gomez-Tortosa E, Ingraham AO, Irizarry MC, et al. Dementia with Lewy bodies. J Am Geriatr Soc 1998;46:1449–1458
43. Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. Ann Neurol 1988;24:50–56
44. Kotzbauer PT, Trojanowsk JQ, Lee VM. Lewy body pathology in Alzheimer's disease. J Mol Neurosci 2001;17:225–232
45. Chui HC, Mack W, Jackson JE, et al. Clinical criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. Arch Neurol 2000;57:191–196
46. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260
47. Wetterling T, Kanitz RD, Borgis KJ. Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). Stroke 1996;27:30–36
48. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology 2005;64:494–500
49. Schneider JA, Wilson RS, Bienias JL, et al. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology 2004;62:1148–1155
50. Kalback W, Esh C, Castano EM, et al. Atherosclerosis, vascular amyloidosis and brain hypoperfusion in the pathogenesis of sporadic Alzheimer's disease. Neurol Res 2004;26:525–539
51. Roher AE, Esh C, Kokjohn TA, et al. Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. Arterioscler Thromb Vasc Biol 2003;23:2055–2062
52. Roher AE, Esh C, Rahman A, et al. Atherosclerosis of cerebral arteries in Alzheimer disease. Stroke 2004;35:2623–2627
53. Hulette C, Nochlin D, McKeel D, et al. Clinical-neuropathologic findings in multi-infarct dementia: a report of six autopsied cases. Neurology 1997;48:668–672
54. Korczyn AD. Mixed dementia—the most common cause of dementia. Ann N Y Acad Sci 2002;977:129–134
55. Nolan KA, Lino MM, Seligmann AW, et al. Absence of vascular dementia in an autopsy series from a dementia clinic. J Am Geriatr Soc 1998;46:597–604
56. Haglund M, Sjobeck M, Englund E. Severe cerebral amyloid angiopathy characterizes an underestimated variant of vascular dementia. Dement Geriatr Cogn Disord 2004;18:132–137
57. Nicoll JA, Yamada M, Frackowiak J, et al. Cerebral amyloid angiopathy plays a direct role in the pathogenesis of Alzheimer's disease. Pro-CAA position statement. Neurobiol Aging 2004;25:589–597
58. Thal DR, Ghebremedhin E, Orantes M, et al. Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol 2003;62:1287–1301
59. Tian J, Shi J, Bailey K, et al. Association between apolipoprotein E e4 allele and arteriosclerosis, cerebral amyloid angiopathy, and cerebral white matter damage in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004;75:696–699
60. Beach TG, Sue L, Scott S, et al. Hippocampal sclerosis dementia with tauopathy. Brain Pathol 2003;13:263–278
61. Leverenz JB, Agustin CM, Tsuang D, et al. Clinical and neuropathological characteristics of hippocampal sclerosis: a community-based study. Arch Neurol 2002;59:1099–1106
62. Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386–2391
63. Hoffman JM, Welsh-Bohmer KA, Hanson M, et al. FDG PET imaging in patients with pathologically verified dementia. J Nucl Med 2000; 41:1920–1928
64. Drzezga A, Grimmer T, Riemenschneider M, et al. Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. J Nucl Med 2005;46:1625–1632
65. Mueller SG, Weiner MW, Thal LJ, et al. The Alzheimer's disease neuroimaging initiative. Neuroimaging Clin N Am 2005;15:869–877
66. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004; 55:306–319
67. Mathis CA, Wang Y, Holt DP, et al. Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. J Med Chem 2003;46:2740–2754
68. Shoghi-Jadid K, Small GW, Agdeppa ED, et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. Am J Geriatr Psychiatry 2002;10:24–35
69. Kung MP, Hou C, Zhuang ZP, et al. Binding of two potential imaging agents targeting amyloid plaques in postmortem brain tissues of patients with Alzheimer's disease. Brain Res 2004;1025:98–105
70. Sunderland T, Linker G, Mirza N, et al. Decreased beta-amyloid1-42 and increased tau levels in cerebrospinal fluid of patients with Alzheimer disease. JAMA 2003;289:2094–2103
71. Khachaturian ZS. Diagnosis of Alzheimer's disease. Arch Neurol 1985; 42:1097–1105
72. Terry RD, Hansen LA, DeTeresa R, et al. Senile dementia of the Alzheimer type without neocortical neurofibrillary tangles. J Neuropathol Exp

Neurol 1987;46:262–268
73. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), pt 2: standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991; 41:479–486
74. Hyman BT, Trojanowski JQ. Consensus recommendations for the post-mortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol 1997;56:1095–1097
75. Beach TG. The history of Alzheimer's disease: three debates. J Hist Med Allied Sci 1987;42:327–349
76. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297: 353–356
77. Neve RL, Robakis NK. Alzheimer's disease: a re-examination of the amyloid hypothesis. Trends Neurosci 1998;21:15–19
78. Sommer B. Alzheimer's disease and the amyloid cascade hypothesis: ten years on. Curr Opin Pharmacol 2002;2:87–92
79. Matsubara E, Shoji M, Abe K, et al. Vascular Amyloidosis in Neurodegenerative Conditions. Drug News Perspect 2002;15:439–444
80. Revesz T, Holton JL, Lashley T, et al. Sporadic and familial cerebral amyloid angiopathies. Brain Pathol 2002;12:343–357
81. Gotz J, Streffer JR, David D, et al. Transgenic animal models of Alzheimer's disease and related disorders: histopathology, behavior and therapy. Mol Psychiatry 2004;9:664–683
82. Nunan J, Small DH. Regulation of APP cleavage by alpha-, beta- and gamma-secretases. FEBS Lett 2000;483:6–10
83. Shi XP, Tugusheva K, Bruce JE, et al. Beta-secretase cleavage at amino acid residue 34 in the amyloid beta peptide is dependent upon gamma-secretase activity. J Biol Chem 2003;278:21286–21294
84. Small DH, McLean CA. Alzheimer's disease and the amyloid beta protein: what is the role of amyloid? J Neurochem 1999;73:443–449
85. Terry RD. The cytoskeleton in Alzheimer disease. J Neural Transm Suppl 1998;53:141–145
86. Bierer LM, Hof PR, Purohit DP, et al. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. Arch Neurol 1995;52:81–88
87. Churcher I. Tau therapeutic strategies for the treatment of Alzheimer's disease. Curr Top Med Chem 2006;6:579–595
88. Chen G, Huang LD, Jiang YM, et al. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. J Neurochem 1999;72:1327–1330
89. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. Proc Natl Acad Sci U S A 1996;93:8455–8459
90. Terry RD, Peck A, DeTeresa R, et al. Some morphometric aspects of the brain in senile dementia of the Alzheimer type. Ann Neurol 1981; 10:184–192
91. Hyman BT, Van Hoesen GW, Damasio AR, et al. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 1984;225:1168–1170
92. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995;375:754–760
93. Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. Ann Neurol 1985;17:278–282
94. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995; 269:973–977
95. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science 1992;256:184–185
96. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–923
97. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993;43:1467–1472
98. Gerdes LU, Klausen IC, Sihm I, et al. Apolipoprotein E polymorphism in a Danish population compared to findings in 45 other study populations around the world. Genet Epidemiol 1992;9:155–167
99. Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world: is APOE*4 a 'thrifty' allele? Ann Hum Genet 1999;63:301–310
100. Zekraoui L, Lagarde JP, Raisonnier A, et al. High frequency of the apolipoprotein E *4 allele in African pygmies and most of the African populations in sub-Saharan Africa. Hum Biol 1997;69:575–581
101. Basun H, Grut M, Winblad B, et al. Apolipoprotein epsilon 4 allele and disease progression in patients with late-onset Alzheimer's disease. Neurosci Lett 1995;183:32–34
102. Dal FG, Rasmusson DX, Brandt J, et al. Apolipoprotein E genotype and rate of decline in probable Alzheimer's disease. Arch Neurol 1996;53:345–350
103. Gomez-Isla T, West HL, Rebeck GW, et al. Clinical and pathological correlates of apolipoprotein E epsilon 4 in Alzheimer's disease. Ann Neurol 1996;39:62–70
104. Kurz A, Egensperger R, Haupt M, et al. Apolipoprotein E epsilon 4 allele, cognitive decline, and deterioration of everyday performance in Alzheimer's disease. Neurology 1996;47:440–443
105. Growdon JH, Locascio JJ, Corkin S, et al. Apolipoprotein E genotype does not influence rates of cognitive decline in Alzheimer's disease. Neurology 1996;47:444–448
106. Craft S, Teri L, Edland SD, et al. Accelerated decline in apolipoprotein E-epsilon4 homozygotes with Alzheimer's disease. Neurology 1998;51: 149–153
107. Jonker C, Schmand B, Lindeboom J, et al. Association between apolipoprotein E epsilon4 and the rate of cognitive decline in community-dwelling elderly individuals with and without dementia. Arch Neurol 1998;55:1065–1069
108. Caselli RJ, Graff-Radford NR, Reiman EM, et al. Preclinical memory decline in cognitively normal apolipoprotein E-epsilon4 homozygotes. Neurology 1999;53:201–207
109. Caselli RJ, Osborne D, Reiman EM, et al. Preclinical cognitive decline in late middle-aged asymptomatic apolipoprotein E-e4/4 homozygotes: a replication study. J Neurol Sci 2001;189:93–98
110. Baxter LC, Caselli RJ, Johnson SC, et al. Apolipoprotein E epsilon 4 affects new learning in cognitively normal individuals at risk for Alzheimer's disease. Neurobiol Aging 2003;24:947–952
111. Caselli RJ, Reiman EM, Osborne D, et al. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. Neurology 2004;62:1990–1995
112. Sorbi S, Nacmias B, Piacentini S, et al. ApoE as a prognostic factor for post-traumatic coma. Nat Med 1995;1:852
113. Jordan BD, Relkin NR, Ravdin LD, et al. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. JAMA 1997; 278:136–140
114. Friedman G, Froom P, Sazbon L, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology 1999;52:244–248
115. Alberts MJ, Graffagnino C, McClenny C, et al. ApoE genotype and survival from intracerebral haemorrhage. Lancet 1995;346:575
116. McCarron MO, Muir KW, Weir CJ, et al. The apolipoprotein E epsilon4 allele and outcome in cerebrovascular disease. Stroke 1998; 29:1882–1887
117. McCarron MO, Hoffmann KL, DeLong DM, et al. Intracerebral hemorrhage outcome: apolipoprotein E genotype, hematoma, and edema volumes. Neurology 1999;53:2176–2179
118. Horsburgh K, McCarron MO, White F, et al. The role of apolipoprotein E in Alzheimer's disease, acute brain injury and cerebrovascular disease: evidence of common mechanisms and utility of animal models. Neurobiol Aging 2000;21:245–255
119. Harris FM, Brecht WJ, Xu Q, et al. Carboxyl-terminal-truncated apolipoprotein E4 causes Alzheimer's disease-like neurodegeneration and behavioral deficits in transgenic mice. Proc Natl Acad Sci U S A 2003; 100:10966–10971
120. Brecht WJ, Harris FM, Chang S, et al. Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. J Neurosci 2004;24:2527–2534
121. Huang Y, Weisgraber KH, Mucke L, et al. Apolipoprotein E: diversity of cellular origins, structural and biophysical properties, and effects in Alzheimer's disease. J Mol Neurosci 2004;23:189–204
122. Handelmann GE, Boyles JK, Weisgraber KH, et al. Effects of apolipoprotein E, beta-very low density lipoproteins, and cholesterol on the extension of neurites by rabbit dorsal root ganglion neurons in vitro. J Lipid Res 1992;33:1677–1688
123. Nathan BP, Bellosta S, Sanan DA, et al. Differential effects of

apolipoproteins E3 and E4 on neuronal growth in vitro. Science 1994; 264:850–852
124. Bellosta S, Nathan BP, Orth M, et al. Stable expression and secretion of apolipoproteins E3 and E4 in mouse neuroblastoma cells produces differential effects on neurite outgrowth. J Biol Chem 1995;270: 27063–27071
125. Ertekin-Taner N, Graff-Radford N, Younkin LH, et al. Linkage of plasma Abeta42 to a quantitative locus on chromosome 10 in late-onset Alzheimer's disease pedigrees. Science 2000;290:2303–2304
126. Wu WS, Holmans P, Wavrant-DeVrieze F, et al. Genetic studies on chromosome 12 in late-onset Alzheimer disease. JAMA 1998;280: 619–622
127. Papassotiropoulos A, Streffer JR, Tsolaki M, et al. Increased brain beta-amyloid load, phosphorylated tau, and risk of Alzheimer disease associated with an intronic CYP46 polymorphism. Arch Neurol 2003; 60:29–35
128. Johansson A, Katzov H, Zetterberg H, et al. Variants of CYP46A1 may interact with age and APOE to influence CSF Abeta42 levels in Alzheimer's disease. Hum Genet 2004;114:581–587
129. Wang B, Zhang C, Zheng W, et al. Association between a T/C polymorphism in intron 2 of cholesterol 24S-hydroxylase gene and Alzheimer's disease in Chinese. Neurosci Lett 2004;369:104–107
130. Papassotiropoulos A, Fountoulakis M, Dunckley T, et al. Genetics, transcriptomics, and proteomics of Alzheimer's disease. J Clin Psychiatry 2006;67:652–670
131. Nalbantoglu J, Gilfix BM, Bertrand P, et al. Predictive value of apolipoprotein E genotyping in Alzheimer's disease: results of an autopsy series and an analysis of several combined studies. Ann Neurol 1994; 36:889–895
132. Relkin NR, Kwon YJ, Tsai J, et al. The National Institute on Aging/ Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease. Ann N Y Acad Sci 1996;802:149–176
133. Roberts JS, Cupples LA, Relkin NR, et al. Genetic risk assessment for adult children of people with Alzheimer's disease: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. J Geriatr Psychiatry Neurol 2005;18:250–255
134. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. N Engl J Med 1996;334:752–758
135. Reiman EM, Caselli RJ, Chen K, et al. Declining brain activity in cognitively normal apolipoprotein E epsilon 4 heterozygotes: A foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease. Proc Natl Acad Sci U S A 2001;98: 3334–3339
136. Reiman EM, Caselli RJ, Alexander GE, et al. Tracking the decline in cerebral glucose metabolism in persons and laboratory animals at genetic risk for Alzheimer's disease. Clin Neurosci Res 2001;1:194–206
137. Reiman EM, Chen K, Alexander GE, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci U S A 2004;101:284–289
138. Caselli RJ, Graff-Radford NR, Reiman EM, et al. Preclinical memory decline in cognitively normal apolipoprotein E-epsilon4 homozygotes. Neurology 1999;53:201–207
139. Caselli RJ, Osborne D, Reiman EM, et al. Preclinical cognitive decline in late middle-aged asymptomatic apolipoprotein E-e4/4 homozygotes: a replication study. J Neurol Sci 2001;189:93–98
140. Baxter LC, Caselli RJ, Johnson SC, et al. Apolipoprotein E epsilon 4 affects new learning in cognitively normal individuals at risk for Alzheimer's disease. Neurobiol Aging 2003;24:947–952
141. Caselli RJ, Reiman EM, Osborne D, et al. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. Neurology 2004;62:1990–1995
142. Caselli RJ, Reiman EM, Hentz JG, et al. A distinctive interaction between memory and chronic daytime somnolence in asymptomatic APOE e4 homozygotes. Sleep 2002;25:447–453
143. Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50:136–145
144. Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999;318:633–638
145. Raskind MA, Peskind ER, Wessel T, et al. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000; 54:2261–2268
146. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–1341
147. Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50:136–145
148. Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999;318:633–638
149. Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1154–1166
150. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD005593
151. Lleo A, Greenberg SM, Growdon JH. Current pharmacotherapy for Alzheimer's disease. Annu Rev Med 2006;57:513–533
152. Rogers SL, Doody RS, Pratt RD, et al. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open-label study. Eur Neuropsychopharmacol 2000; 10:195–203
153. Raskind MA, Peskind ER, Truyen L, et al. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol 2004;61:252–256
154. Feldman H, Gauthier S, Hecker J, et al. Economic evaluation of donepezil in moderate to severe Alzheimer disease. Neurology 2004;63: 644–650
155. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005; 293:596–608
156. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335–2341
157. Tune LE. Depression and Alzheimer's disease. Depress Anxiety 1998; 8(suppl 1):91–95
158. Schenck CH, Mahowald MW, Kim SW, et al. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. Sleep 1992;15:226–235
159. Salzman C. Treatment of the agitation of late-life psychosis and Alzheimer's disease. Eur Psychiatry 2001;16(suppl 1):25s–28s
160. Devanand DP. Behavioral complications and their treatment in Alzheimer's disease. Geriatrics 1997;52(suppl 2):S37–S39
161. Shelton PS, Hocking LB. Zolpidem for dementia-related insomnia and nighttime wandering. Ann Pharmacother 1997;31:319–322
162. Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. JAMA 2001;285:2888–2890
163. Gottlieb DJ, DeStefano AL, Foley DJ, et al. APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the Sleep Heart Health Study. Neurology 2004;63:664–668
164. Dubinsky RM, Stein AC, Lyons K. Practice parameter: risk of driving and Alzheimer's disease (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2000;54:2205–2211
165. Caselli RJ. Visual syndromes as the presenting feature of degenerative brain disease. Semin Neurol 2000;20:139–144
166. Drachman DA, Swearer JM. Driving and Alzheimer's disease: the risk of crashes. Neurology 1993;43:2448–2456
167. Logsdon RG, Teri L, Larson EB. Driving and Alzheimer's disease. J Gen Intern Med 1992;7:583–588
168. Fitten LJ, Perryman KM, Wilkinson CJ, et al. Alzheimer and vascular dementias and driving: a prospective road and laboratory study. JAMA 1995;273:1360–1365
169. Hunt LA, Murphy CF, Carr D, et al. Reliability of the Washington University Road Test: a performance-based assessment for drivers with dementia of the Alzheimer type. Arch Neurol 1997;54:707–712
170. Duchek JM, Hunt L, Ball K, et al. Attention and driving performance in Alzheimer's disease. J Gerontol B Psychol Sci Soc Sci 1998;53: 130–141
171. Rebok GW, Keyl PM, Bylsma FW, et al. The effects of Alzheimer

  © COPYRIGHT 2006 PHYSICIANS POSTGRADUATE PRESS, INC.

disease on driving-related abilities. Alzheimer Dis Assoc Disord 1994; 8:228–240
172. Rizzo M, Reinach S, McGehee D, et al. Simulated car crashes and crash predictors in drivers with Alzheimer disease. Arch Neurol 1997; 54:545–551
173. Cox DJ, Quillian WC, Thorndike FP, et al. Evaluating driving performance of outpatients with Alzheimer disease. J Am Board Fam Pract 1998;11:264–271
174. Drachman DA, Swearer JM. Driving and Alzheimer's disease: the risk of crashes. Neurology 1993;43:2448–2456
175. Logsdon RG, Teri L, Larson EB. Driving and Alzheimer's disease. J Gen Intern Med 1992;7:583–588
176. Hunt LA, Murphy CF, Carr D, et al. Reliability of the Washington University Road Test: a performance-based assessment for drivers with dementia of the Alzheimer type. Arch Neurol 1997;54:707–712
177. Fox GK, Bowden SC, Bashford GM, et al. Alzheimer's disease and driving: prediction and assessment of driving performance. J Am Geriatr Soc 1997;45:949–953
178. Mendez MF. Dementia and guns. J Am Geriatr Soc 1996;44:409–410
179. Spangenberg KB, Wagner MT, Hendrix S, et al. Firearm presence in households of patients with Alzheimer's disease and related dementias. J Am Geriatr Soc 1999;47:1183–1186
180. Mittelman MS, Roth DL, Coon DW, et al. Sustained benefit of supportive intervention for depressive symptoms in caregivers of patients with Alzheimer's disease. Am J Psychiatry 2004;161:850–856
181. Smith GE, Kokmen E, O'Brien PC. Risk factors for nursing home placement in a population-based dementia cohort. J Am Geriatr Soc 2000;48:519–525
182. Gaugler JE, Edwards AB, Femia EE, et al. Predictors of institutionalization of cognitively impaired elders: family help and the timing of placement. J Gerontol B Psychol Sci Soc Sci 2000;55:247–255
183. Knopman D, Schneider L, Davis K, et al. Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, Tacrine Study Group. Neurology 1996;47:166–177
184. Geldmacher DS, Provenzano G, McRae T, et al. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003;51:937–944
185. Schulz R, O'Brien AT, Bookwala J, et al. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. Gerontologist 1995;35:771–791
186. Mittelman MS, Roth DL, Coon DW, et al. Sustained benefit of supportive intervention for depressive symptoms in caregivers of patients with Alzheimer's disease. Am J Psychiatry 2004;161:850–856
187. Citron M. Strategies for disease modification in Alzheimer's disease. Nat Rev Neurosci 2004;5:677–685
188. Ritchie CW, Bush AI, Mackinnon A, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. Arch Neurol 2003;60:1685–1691
189. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 1999;400:173–177
190. Orgogozo JM, Gilman S, Dartigues JF, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology 2003;61:46–54
191. Siemers ER, Quinn JF, Kaye J, et al. Effects of a gamma-secretase inhibitor in a randomized study of patients with Alzheimer disease. Neurology 2006;66:602–604
192. Lytle ME, Vander BJ, Pandav RS, et al. Exercise level and cognitive decline: the MoVIES project. Alzheimer Dis Assoc Disord 2004;18: 57–64
193. Gatz M. Educating the brain to avoid dementia: can mental exercise prevent Alzheimer disease? PLoS Med 2005;2:e7
194. Morris MC, Evans DA, Bienias JL, et al. Vitamin E and cognitive decline in older persons. Arch Neurol 2002;59:1125–1132
195. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61:82–88
196. Commenges D, Scotet V, Renaud S, et al. Intake of flavonoids and risk of dementia. Eur J Epidemiol 2000;16:357–363
197. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002;287:3223–3229
198. Kalmijn S, Feskens EJ, Launer LJ, et al. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 1997;145:33–41
199. Clarke R, Smith AD, Jobst KA, et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998;55:1449–1455
200. Ringman JM, Frautschy SA, Cole GM, et al. A potential role of the curry spice curcumin in Alzheimer's disease. Curr Alzheimer Res 2005;2:131–136
201. Luchsinger JA, Tang MX, Shea S, et al. Caloric intake and the risk of Alzheimer disease. Arch Neurol 2002;59:1258–1263
202. Scarmeas N, Stern Y, Tang MX, et al. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006;59:912–921
203. Ruitenberg A, van Swieten JC, Witteman JC, et al. Alcohol consumption and risk of dementia: the Rotterdam Study. Lancet 2002;359: 281–286
204. Sparks DL, Sabbagh M, Connor D, et al. Statin therapy in Alzheimer's disease. Acta Neurol Scand Suppl 2006;185:78–86
205. Birkenhager WH, Staessen JA. Antihypertensives for prevention of Alzheimer's disease. Lancet Neurol 2006;5:466–468
206. Sun MK, Alkon DL. Links between Alzheimer's disease and diabetes. Drugs Today (Barc) 2006;42:481–489
207. McGeer PL, McGeer EG. Anti-inflammatory drugs in the fight against Alzheimer's disease. Ann N Y Acad Sci 1996;777:213–220
208. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2651–2662
209. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;291:2947–2958

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Alzheimer's Disease and Related Disorders section. Please contact Eric M. Reiman, M.D., at Eric.Reiman@bannerhealth.com.

