

ALZHEIMER DISEASE: FROM EARLIEST SYMPTOMS TO END STAGE

RICHARD C. MOHS
VAHRAM HAROUTUNIAN

INTRODUCTION TO THE NATURAL HISTORY

Alzheimer disease (AD) is a progressive, degenerative brain disease that is the most common cause of dementia in elderly persons. Clinically, patients with AD have impairments in memory, language, praxis, and other cognitive functions that develop very gradually but progress relentlessly. Longitudinal studies leading to autopsy have shown that the most common neuropathologic findings in elderly patients with these symptoms are neuritic plaques (NPs) and neurofibrillary tangles (NFTs). Modern diagnostic criteria for AD recognize that AD is both a clinical and pathologic entity. By definition, all patients with AD must have dementia, a progressive loss of memory, and at least one other cognitive function that is sufficiently severe to interfere with daily functioning. To differentiate AD from other acquired neuropsychiatric conditions associated with cognitive impairment, the clinical diagnosis of AD is only made when no other conditions could account for the patient's progressive cognitive impairment. Patients who meet the clinical criteria for AD are very likely to have the characteristic neuropathologic features as well. Sometimes, however, the clinical diagnosis is not confirmed at autopsy, and hence the most widely used criteria for AD reserve the term *definite AD* for those patients in whom both clinical and neuropathologic data support the diagnosis of AD.

Although progressive cognitive impairment is the core or defining characteristic of AD clinically, patients with this disease have other symptoms as well. Many patients also have other neuropsychiatric symptoms including agitation, psychosis, depressed mood, and personality change. These other symptoms are not necessary for a diagnosis of AD and tend to be quite variable both within a given patient and from one patient to another. When they are present, these symptoms can be a major problem for caregivers of

AD patients, and behavioral problems have been linked to an increased need for health services including nursing home care.

The first definite symptoms of AD are often quite mild and are difficult to differentiate from the mild memory loss that is a frequent consequence of normal or usual aging. Inevitably, however, the degenerative changes of AD become sufficiently severe so the patient has difficulty with daily functioning. The functional change can be observed first in the performance of cognitively demanding tasks such as handling money, remembering appointments, following directions, and using appliances. As the disease progresses and the patient's cognitive abilities deteriorate, the patient has difficulty in more functional domains including the basic activities of daily living such as feeding, toileting, dressing, and personal hygiene. In the later stages of AD, patients are often unable to remember even very simple things, have great difficulty talking and understanding language, and may be confined to bed or to a chair. The average life expectancy of a patient with AD after the initial diagnosis is approximately 10 years, but with a great deal of variability around that mean.

In the sections that follow, we review studies of the development of the neurobiological changes responsible for AD. Later, we briefly review the epidemiology of AD and review in greater detail the development of the disease clinically. In each section, we emphasize the need to understand AD from a longitudinal perspective because both the underlying neurobiology and clinical presentation of the illness vary substantially across the course of illness. Because of intense recent interest in understanding the very early development of AD to develop preventive therapies, our presentation emphasizes recent findings on the earliest manifestations of disease.

NEUROBIOLOGICAL STUDIES ACROSS THE SEVERITY SPECTRUM

It has already been noted that the definitive diagnosis of AD depends on neuropathologic changes that characterize

the disease. No single neuropathologic lesion is in itself adequate for the diagnosis of AD; rather, the neuropathologic diagnosis of AD is based on the presence of multiple AD-related lesions, the density of these lesions relative to the age of the subject, and the absence of lesions characteristic of other neuropathologic diseases. The absolute weight of the brain is decreased relative to normal controls, but this decrease is generally less than 10% relative to age-matched controls, and it is neither diagnostic of nor specific to AD (1). Gross examination of the brain in AD also reveals significant apparent atrophy, widening of the sulci, and erosion of the gyri, but these changes also reflect advanced age with significant overlap between AD and normal elderly controls. However, the atrophy of the cortex is associated with significant reductions in the numbers of neurons (2,3). For example, Terry et al. reported 40% to 46% losses of large neurons in the frontal and temporal cortices of specimens derived from patients with AD (4). Similarly, Gomez-Isla and colleagues (5,6), using unbiased stereologic sampling techniques, reported approximately 50% losses in neurons of the superior temporal sulcus with even more pronounced losses in specific cortical laminae. These neuronal losses were observed not only in brain specimens from patients with severe dementia, but also in specimens derived from patients with relatively mild or questionable dementia. The magnitude of neuronal loss increases systematically with increasing dementia severity and increasing disease duration. Neuronal degeneration is not restricted to the cortex, but it is also reflected in neuronal losses in subcortical nuclei such as the nucleus basalis of Meynert (7) (the cells of origin of the cholinergic input to the cerebral cortex), the locus ceruleus, and raphe aminergic nuclei (8,9). Neuronal loss in these subcortical structures, especially in the nucleus basalis of Meynert (10), has also been found to correlate significantly with dementia severity and cognitive deficits.

Neuronal loss and degeneration are accompanied by significant decreases in markers of synaptic density. Although synaptic markers such as synaptophysin are reduced significantly in the cerebral cortex, especially the frontal and parietal cortices and in the hippocampus, with increasing age (11), further losses are encountered in AD, whether assessed by immunohistochemical techniques or by direct assessment of synaptic specializations and profiles (3,12–14). The loss of synaptophysin immunoreactivity in the frontal and parietal cortices, and in the hippocampus, is among the strongest correlates of dementia severity (10,15,16). These losses and correlations with cognitive function are not only evident at the immunohistochemical level, but they have also been observed with quantitative enzyme-linked immunosorbent assay techniques (10). This loss of synaptic markers is not merely a reflection of the degeneration of the cortical neurons noted earlier, but it also reflects the loss of presynaptic terminals and neuropeptide- and neurotransmitter-containing vesicles.

Various specific lesions have been found to be associated

with AD. The most prominent are NPs and NFTs. However, these lesions are not exclusively associated with AD. Age-related accumulations of NPs and diffuse plaques have been noted in elderly persons who are otherwise normal. Similarly, NFTs have been found in the brains of nondemented elderly persons and in association with non-AD-like neurodegenerative diseases (17). Although NP and NFT lesions can be present in diseases other than AD, other markers and clinical phenotypes can be used to distinguish among them, and the presence of NPs and NFTs in the absence of other confounding neuropathologic lesions provides the basis for the diagnosis of AD.

NPs are extracellular deposits of varying sizes with an amyloid β -peptide core ($A\beta$) and neuritic inclusions. $A\beta$ is a 40 to 43 amino acid long peptide that is generated from a larger peptide (Alzheimer amyloid precursor protein or APP) by two cleavage events (18). The cleavage mechanisms that lead to the production of $A\beta$ from APP are under intense investigation. β -Amyloid cleavage enzyme was isolated and cloned and proposed as the enzyme responsible for cleavage at the N-terminus (19–21). Cleavage at the C-terminus is attributed to an as yet unidentified enzyme termed γ -secretase. Some evidence suggests that presenilin 1 may be the γ -secretase (22), but this hypothesis is still under investigation. That $A\beta$ deposition plays a critical role in the pathogenesis of AD was recognized with the accumulation of evidence showing that mutations in the APP gene, as well as mutations in the gene encoding for presenilin 1 and 2, were invariably associated with AD (23,24). Studies in transgenic mice demonstrated that the introduction of these mutations leads to the development of $A\beta$ plaques and learning and memory deficits in some mutants (25–27).

Despite the clear evidence implicating NP deposition in the pathogenesis of AD, few studies have addressed the relationship of NP deposition with the symptoms of AD (dementia) during the early phases of the disease. Ascertainment of the relationship between specific pathologic lesions and symptoms of AD has been difficult, because most studies have focused on the neuropathology of AD at the terminal stages of the disease, when dementia has been fully developed and neuropathologic lesions have been profuse. Studies have suggested that increases in the densities of neocortical NPs occur very early during the course of cognitive deterioration (6,10,28–32), and they may be among the initial pathologic events in the development of AD (31). In some of these studies, brain specimens were grouped according to the severity of dementia before death according to the Clinical Dementia Rating (CDR) scale. The density of NPs and $A\beta$ immunoreactivity were then quantified in different brain regions. These studies showed that increases in NP density and quantitatively measured $A\beta$ immunoreactivity are evident even in those patients who die at the earliest stages of dementia, when dementia severity is very mild or even questionable. The density of NPs and $A\beta$

immunoreactivity then increase systematically as a function of increasing dementia severity. In one study (29), elevated levels of A β -42 were detected in multiple neocortical regions before NFTs and significant immunoreactivity to abnormal tau (see later) could be demonstrated in the same cortical regions. Increases in NP density and A β immunoreactivity were observed in cases of mild dementia before the density of neuropathologic lesions was high enough for the patients to meet the threshold criteria for the definitive diagnosis of AD.

NFTs constitute the second hallmark of AD neuropathology. Immunohistochemical and biochemical studies have shown that NFTs consist of paired helical filaments that are abnormal aggregates of abnormally folded (33,34) or phosphorylated (35,36) forms of the microtubule-associated protein tau. The progressive involvement and distribution of NFTs to different brain regions have been used to stage the neuropathologic severity of AD (37,38). These studies have suggested that the first signs of NFT are found within the entorhinal cortex, followed by the hippocampus, and the eventual involvement of virtually all regions of the isocortex. There is also clear evidence that the density and severity of NFTs increase as a function of increasing disease duration (5,6). Thus, both the density of NFTs in any given brain region and the regions of the brain affected increase with increasing disease duration. In a study identical to that described earlier, study subjects were grouped on the basis of the severity of dementia before death, and the density of NFT-bearing neurons in different brain regions was quantified as a function of dementia severity (39). The density of NFTs in all brain regions increased as a function of increasing dementia severity. However, moderate NFT involvement was documented in the entorhinal cortex of elderly patients with no clinical evidence of dementia (see also ref. 40). Neocortical NFTs were abundant only in patients with moderate to severe dementia, and NFT density increased as a function of increasing dementia severity. Although neocortical NFTs were present in patients with moderate dementia, NFT abundance was low or absent in patients with mild or questionable dementia. Similar findings have been reported in other studies (10,11,40). These studies suggest that NFTs are most abundant in the entorhinal cortex, where they can be observed in nondemented elderly subjects as well as in patients with AD. NFTs involve neocortical structures later in the course of the AD and are associated with significant dementia. As dementia severity increases, so does the density of neocortical NFTs. This correlation of NFT density with dementia severity is not restricted to the neocortex and to the hippocampus, but it also applies to the subcortical nuclei, such as the forebrain cholinergic nucleus basalis of Meynert (15). Thus, NFTs are a significant neuropathologic feature of AD and contribute to the progression of dementia.

In addition to the neuropathologic lesions associated with AD, significant deficits in neurochemical functions

and indices have been observed (41). Chief among these neurochemical deficits are deficits in neocortical indices of cholinergic function and decreases in the concentrations of several neuropeptides such as somatostatin and corticotropin-releasing hormone (42). Deficits in several other neurochemicals and neurotransmitters such as norepinephrine and serotonin have also been reported, but their alterations are not as profound and do not appear to be as consistently observed (41,43,44). Deficits in the activity of cholinergic marker enzymes (choline acetyltransferase and acetylcholinesterase) were among the first to be reported in AD (45, 46). Deficits in cortical cholinergic marker enzymes have been among the most consistently replicated neurochemical findings in AD. Some studies have reported that compensatory mechanisms interact with cholinergic enzyme deficits and lead to an up-regulation of high-affinity choline transport (47). Irrespective of compensatory mechanisms that may be engaged, the loss of cortical cholinergic enzyme activity is associated with severe degeneration of cholinergic neurons in the basal forebrain including the neocortically projecting neurons of the nucleus basalis of Meynert (7). The discovery of these profound forebrain cholinergic system deficits and the growing understanding of the role of the forebrain cholinergic system in learning and memory (48) were pivotal to the development of the current therapeutic strategies in AD (49), which focus on the restoration of these cholinergic deficits by inhibiting the activity of the acetylcholine catabolic enzyme, acetylcholinesterase.

As with neuropathologic studies of AD, most postmortem studies assessing cholinergic markers in AD were derived from patients with end-stage dementia. Those few studies in which brain biopsies were obtained and cholinergic markers were assessed ante mortem were generally restricted to patients who have a very early onset of dementia or to patients with relatively advanced dementia (50–52). Thus, although deficits in the activity of cholinergic marker enzymes have been shown to correlate significantly with dementia severity (43,53), the question whether these profound deficits in cholinergic markers found in patients with end-stage dementia extend to patients with much earlier disease remained unanswered until recently. Using the same strategy as that described for studying neuropathologic changes in early dementia, Davis and colleagues assigned patients to groups on the basis of their cognitive status at the time of death according to the CDR scale (54). After stratification of subjects to different dementia conditions, the activity of cholinergic marker enzymes was assessed in multiple neocortical regions that encompassed representative regions within the frontal, temporal, parietal, and occipital cortices. Cholinergic marker enzyme activity was profoundly diminished in patients with end-stage, severe dementia, but neither the activity of acetylcholinesterase nor the activity of choline acetyltransferase was reduced in subjects with mild and moderate dementia. Although it can be argued that adaptive changes compensate for cholinergic

deficits in mild dementia (47), the most parsimonious interpretation of these results is that cholinergic deficits are characteristic of relatively advanced dementia and contribute relatively less to the early phases of cognitive impairment in AD.

Deficits in selected neuropeptides have also been consistently reported in AD (41). The levels of somatostatin (SLI) and corticotropin-releasing factor (CRF) are the most consistently affected (55–57). Deficits in these neuropeptides are often found to be as profound as those observed for the cholinergic marker enzymes and are specific in that not all neuropeptides are diminished in AD cortex (58,59). The CRF deficits are accompanied by the up-regulation of CRF receptors (60), whereas SLI receptors density is either unchanged or down-regulated (56). Evidence of the relationship of the concentration of these neuropeptides to the severity of dementia has been sparse. Some insight into CRF concentrations in earlier stages of AD has been gained from negative correlations between CRF levels and duration of illness (61), as well as from studies of cerebrospinal fluid (62). Correlations between the severity of Alzheimer dementia and cerebrospinal fluid CRF have been found, suggesting that the CRF deficiency may be a relatively early marker of AD. This relationship has not been observed consistently (63,64), however. Postmortem studies of CRF and SLI concentrations in the cortices of subjects stratified to groups on the basis of their cognitive status at the time of death have suggested that although the concentrations of both neuropeptides are significantly and severely diminished in patients with severe or terminal dementia, only the levels of CRF are significantly altered in patients with mild to moderate dementia (65).

In the past few years, many epidemiologic studies have addressed the possible protective effect of antiinflammatory drug use with regard to AD (66,67). At a molecular level, it is apparent that an inflammatory response accompanies the neuropathologic features of AD (66–69). There is clear evidence of an acute-phase response with up-regulation of inflammatory cytokines such as interleukin 1 (IL-1) and IL-6 and tumor necrosis factor- α , accompanied by an increase in acute-phase proteins such as α 1-antichymotrypsin and α ₂-macroglobulin (66). The complement system is active in the AD brain (70, 71), with generation of the lytic membrane attack complex and presumably with release of anaphylatoxins. Up-regulation of cyclooxygenase 2 in AD neurons (69) suggests that inflammatory lipids may also be involved in the pathogenesis of the disease. It has been hypothesized that inflammatory responses can be autotoxic to neurons and may exacerbate the fundamental pathology of AD (72). The epidemiologic studies with antiinflammatory agents and a prospective study suggesting some slowing of disease progression after indomethacin treatment support a role for inflammatory processes in AD progression (66). Although studies seeking direct evidence of the role of inflammatory processes in the progression of AD and demen-

tia have been initiated only recently (73), one study has examined cytokine gene expression during AD progression. In this study, cytokine gene expression (IL-6 mRNA) in the hippocampus was found to increase as dementia severity progressed from moderate (CDR 2) to severe (CDR 5). Neither the epidemiologic studies nor the neurobiological studies directly address the cause and effect relationship among AD, dementia progression, and inflammatory responses within the brain. These studies do suggest, however, that even if inflammatory responses are not a critical feature of the etiology of AD, they may nevertheless play an important role in mediating the development and progression of dementia.

The results of the studies summarized earlier provide only a very general and global review of the tens of thousands of published reports relevant to the pathogenesis of AD. The results of the more recent studies, especially those that relate to the progression of the disease and dementia, have shed some new light on the pathophysiologic mechanisms involved at the onset of dementia and its progression during the disease process. These relatively recent findings have suggested that, in contrast to some earlier views, the deposition of amyloid plaques is integral to the onset and progression of dementia, and, at least in some brain regions such as the cerebral cortex, they may precede the involvement of some of the other prominent deficits and lesions (e.g., NFTs and cholinergic and neuropeptidergic deficits) characteristic of later stages of the disease. These results have also emphasized that many different lesions contribute to AD neuropathology, and each lesion (NP, NFT, neuronal loss, synaptic loss, cholinergic deficit, neuropeptide deficit, inflammatory response, and countless others) contributes significantly to the dementia symptoms of AD. Conversely, these studies have shown that AD is not characterized by random or general neural system failures, but rather that the pathologic features of AD appear to follow a course of progressive involvement of different neuronal systems, the characteristics of which are only now beginning to be elucidated.

CLINICAL AND NEUROPSYCHOLOGIC STUDIES

Epidemiologic Studies of Persons at Risk

Precise estimates of the proportion of dementia cases that are attributable to AD are difficult to obtain because few population-based studies obtain autopsy data that would enable a definitive diagnosis of AD. In most large-scale autopsy series, AD lesions are the primary neuropathologic finding in more than 50% of all dementia cases (74). Studies using clinical criteria also find that AD accounts for more than 50% of all dementias, with mixed AD plus vascular dementia and AD plus parkinsonism accounting for significant proportions of the remaining cases (75). Pure vascular

dementia and Lewy body dementia are also found with some regularity, but they are both far less common than AD. Because of the high prevalence of AD among dementia cases, the epidemiology of dementia in old age is largely the epidemiology of AD. Because AD is so much more common than other types of old-age dementia, some clinical guidelines have argued that AD should be treated as a diagnosis of inclusion rather than one of exclusion (76); that is, an older person with dementia should be diagnosed with AD unless there is substantial clinical evidence supporting another cause of the dementia.

The prevalence of AD rises dramatically with age, and age is the most potent risk factor for AD. Less than 1% of new cases of AD are found in persons younger than age 65 years (77), and the prevalence of AD rises steadily after that. By age 90, approximately 35% of persons remaining alive will have AD (77). Men and women are equally vulnerable to AD, but because women live longer than men on average, there are more women than men with AD. Studies looking at different ethnic and cultural groups have found that AD is common in elderly persons from all ethnic and socioeconomic backgrounds, but there may be some Asian ethnic groups who are less vulnerable to AD (78). Environmental risk factors for AD have been difficult to identify, but there is some evidence that persons with higher educational attainment are less likely to develop AD in old age (79). Neurobiological mechanisms that may account for the protective effect of education have not been elucidated, but it is possible that persons with more education have a greater reserve of brain capacity that enables those persons to remain cognitively intact for longer periods of time during the early stages of AD.

Certain genetic factors have been identified that contribute to the development of AD. Specific genetic mutations that cause AD have been identified in the gene coding for the amyloid precursor protein, in the presenilin 1 gene, and in the presenilin 2 gene (24,80). Persons who inherit one of these mutations develop AD when they are quite young, often as early as age 40 to 50 years. In families carrying one of these mutations, the inheritance of AD follows the classic pattern of autosomal dominant inheritance, with 50% of each generation developing the disease. Investigations of these mutations are very important because of the information they provide about possible pathophysiologic mechanisms leading to the development of plaques, tangles, cell loss, and dementia. From a population standpoint, however, these genetically determined cases of AD are of less interest because they constitute a small fraction of all cases observed clinically. Most estimates are that less than 2% of all AD cases result from specific genetic mutations (80).

Family (81) and population (82) studies have demonstrated that persons who carry the $\epsilon 4$ form of the apolipoprotein E (Apo E) gene (*APOE*) have a greater likelihood of developing AD than do persons who carry only the $\epsilon 3$ and the $\epsilon 2$ forms. Apo E is a cholesterol-transporting pro-

tein that is coded by a gene on chromosome 14. The gene has three allelic forms, $\epsilon 3$, which is by far the most common, and two rarer forms, $\epsilon 2$ and $\epsilon 4$. Persons carrying the $\epsilon 4$ form are at increased risk of developing AD, particularly between the ages of 65 and 75 years. The mechanism by which *APOE* genotype influences the risk of AD is currently under investigation. From a clinical standpoint, *APOE* can be useful for identifying persons at increased risk of developing AD. It is not useful in routine diagnostic evaluations, however, because many patients who develop AD do not carry the $\epsilon 4$ allele, and some who do carry the high-risk form of *APOE* do not develop AD (82). There is extensive research to identify other common genes that influence the likelihood of developing AD, but none have been identified that consistently associate with the risk of AD as *APOE* genotype does.

Predictive Neuropsychological Deficits

AD is a progressive disease with insidious onset in which the underlying neurodegenerative changes probably begin years before clinical symptoms are obvious. Studies of populations at risk of developing AD have been conducted to determine whether there are changes in cognitive function that can be detected with neuropsychological tests before patients meet clinical criteria for the diagnosis of AD. For these studies, persons who are cognitively normal but who are at increased risk of developing AD, usually because of old age, are followed longitudinally with a structured battery of neuropsychological tests. After a period of 1 to 5 years, the baseline performance of patients who have subsequently been diagnosed with AD is compared with the remainder of the population that has remained free of dementia. Several studies using this model have demonstrated consistently that impairment in memory is significantly worse at baseline in those persons who subsequently are diagnosed with AD (83–85). In most instances, the memory tests most impaired before diagnosis are those measuring delayed recall, that is, recall of newly learned information but after a delay of several minutes during which the subject must perform other cognitive tasks. A deficit in the rate of new learning for verbal material (e.g., a list of words) has also been found to predict subsequent dementia in some studies (85). Language function, particularly difficulty with naming, has also been found to differentiate those persons who subsequently develop dementia from others who remain free of dementia (83). Occasionally, other cognitive tasks such as those placing great demands on executive function and working memory show deficits before the onset of dementia, but memory impairment is uniformly the most pronounced deficit (84).

Evidence indicates that some of the predictive power of poor performance on neuropsychological tests results from the fact that memory deficits are, in part, a subclinical surrogate identifying those at increased risk because of old age or presence of an *APOE* $\epsilon 4$ genotype. Because studies have

clarified that *APOE* genotype may confer additional risk of AD primarily within a certain age range (86), it is likely that *APOE* genotype and neuropsychological test performance are independent predictors of dementia in most instances. Analyses of data from these data on neuropsychological antecedents of dementia have consistently shown that the memory and other deficits cannot be accounted for simply by considering age as a predictor. Rather, it appears that deficits in memory and, to a lesser extent, language and executive function are predictors of subsequent dementia across a broad range of ages and for all *APOE* genotypes.

Longitudinal Studies

Numerous longitudinal studies have documented the progression of cognitive, behavioral, and functional changes throughout the course of illness. As expected, given the studies of populations at risk for AD described earlier, studies of very mild AD have documented that memory impairment is the earliest and most prominent feature of the illness (87). As a consequence, memory measures, particularly those employing a measure of delayed recall memory, are now frequently used to identify persons thought to be in the very earliest stages of AD or who may be at high risk of developing AD. As the disease progresses, deficits in both expressive and receptive language and deficits in praxis and visuospatial ability become quite pronounced. Longitudinal studies have also documented that cognitive deterioration in AD is relentlessly progressive, with little evidence of improvement (88).

Some standard assessment tools have been developed to measure the cognitive deficits in AD in a semiquantitative fashion. Among the most commonly used assessment tools are the Mini-Mental State Examination (89), the Blessed Test of Information, Memory, and Concentration (90), and the Alzheimer's Disease Assessment Scale (91). Each of these instruments includes brief tests to assess dysfunction in cognitive domains typically impaired in AD, particularly memory, language, orientation, and praxis. The Mini-Mental State Examination and the Blessed test are quite brief and are often used as screening instruments in research and clinical practice. The Alzheimer's Disease Assessment Scale was developed as a tool for use in clinical trials and is almost always used as one of the primary efficacy measures in clinical trials of antidementia drugs (49,92). Longitudinal studies with each of these instruments have been performed. Those studies demonstrate that the measured rate of cognitive decline in AD is quite consistent from study to study and across different populations (88,93). In addition, the rate of cognitive decline in AD is curvilinear with time, such that deterioration is quite slow at the start of the illness, is faster during the middle years of illness, and is again slow when patients reach the near terminal phase of the illness. This relationship of rate of deterioration with stage of illness

has important implications for clinical trials of agents that are expected to slow the rate of cognitive deterioration (88, 94).

Factors that may be associated with differences in the rate of cognitive deterioration have been investigated extensively. Apart from the relationship of rate with stage of disease described earlier, no other factors have been found to affect the rate of deterioration consistently. Age, age of disease onset, gender, ethnicity, and *APOE* genotype have all been examined as possible predictors, and none has consistently been shown to affect the rate of decline. Once patients develop the disease, cognitive function deteriorates relentlessly and at approximately the same rate regardless of these variables (88,93,94).

Behavioral disturbances have also been investigated longitudinally, and it is clear that symptoms such as psychosis, agitation, and depressed mood can be very disturbing both to the patient and to caregivers. Because of the importance of these symptoms in patient management, new tools have been developed in an effort to provide reliable and valid assessment of their severity. Commonly used tools include the Neuropsychiatric Inventory (95), the BEHAVE-AD (96), and the noncognitive subscale of the Alzheimer's Disease Assessment Scale (91). In contrast to the cognitive deficits of AD, however, these behavioral disturbances are quite variable from one patient to another and over time in individual patients (95,97). These disturbances are episodic phenomena that wax and wane over the course of AD, with little evidence of progression. Most trials of potential new treatments for AD now include some assessment of these symptoms, and the overall effectiveness of treatments for AD is at least partly determined by the extent to which they improve behavioral symptoms.

By definition, all patients with AD have some impairment in their ability to perform daily activities (98). The assessment of functional ability in patients with dementia includes both an assessment of the basic activities of daily living such as feeding, toileting, dressing, and grooming and an assessment of more cognitively demanding, instrumental activities of daily living such as handling money, using the telephone, performing household chores, and using appliances (99,100). The definition of basic activities of daily living is quite consistent from study to study, but there is much less consensus on the kinds of activities that must be surveyed in any assessment of instrumental activities of daily living. Longitudinal data are consistent, however, in demonstrating that impairments in instrumental activities of daily living appear very early in the course of AD, whereas impairments in basic activities of daily often do not appear until patients are quite cognitively impaired (100,101). Thus, any comprehensive assessment of functional status in AD must include both basic and instrumental activities of daily living.

The longitudinal progression of functional impairment is relentless, and functional abilities, once lost, are rarely

regained (100,101). In this regard, functional impairment follows a progression similar to that of cognitive decline. Correlational studies invariably find a close relationship of functional impairment with the degree of cognitive impairment (101). There is some evidence that the severity of behavioral symptoms, including psychosis and agitation, is associated with some excess disability over that resulting from cognitive impairment, but the contribution of behavioral pathology to functional impairment is relatively small (102). Overall, the trajectory of functional impairment in AD follows the progressive downhill course determined by cognitive loss.

CONCLUDING COMMENT

Development of effective treatments for AD will be facilitated by a detailed understanding of the neurobiological mechanisms underlying the disease at each of its stages. Testing of treatments for AD requires an understanding of the clinical manifestations and consequences of the disease at each of its stages. Studies investigating neurobiological and clinical changes of the disease over its entire course are providing the tools necessary to develop effective interventions for the prevention and treatment of AD.

DISCLAIMER

Dr. Mohs serves as a research consultant to the following companies: Pfizer, Eli Lilly, Janssen, Orth-Biotech, and Forest.

REFERENCES

1. Terry RD. Structural changes in senile dementia of the Alzheimer type. In: Amaducci L, Davison AN, Antuono P, eds. *Aging of the brain and dementia*. New York: Raven, 1980:23–32.
2. Ball M. Neuronal loss, neurofibrillary tangles and granulovacuolar degeneration in the hippocampus with ageing and dementia. *Acta Neuropathol (Berl)* 1977;37:111–118.
3. Masliah E, Terry R, Alford M, et al. Cortical and subcortical patterns of synaptophysin-like immunoreactivity in Alzheimer's disease. *Am J Pathol* 1991;138:235–246.
4. 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.
5. Gomez-Isla T, Hollister R, West H, et al. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol* 1997;41:17–24.
6. Gomez-Isla T, Price JL, McKeel DW Jr, et al. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J Neurosci* 1996;16:4491–4500.
7. Whitehouse PJ, Price DL, Struble RG, et al. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 1982;215:1237–1239.
8. Chan-Palay V, Asan E. Alterations in catecholamine neurons of the locus coeruleus in senile dementia of the Alzheimer type and in Parkinson's disease with and without dementia and depression. *J Comp Neurol* 1989;287:373–392.
9. Zweig RM, Ross CA, Hedreen JC, et al. The neuropathology of aminergic nuclei in Alzheimer's disease. *Ann Neurol* 1988;24:233–242.
10. Dickson DW, Crystal HA, Bevona C, et al. Correlations of synaptic and pathological markers with cognition of the elderly. *Neurobiol Aging* 1995;16:285–298.
11. Nagy Z, Esiri MM, Jobst KA, et al. Relative roles of plaques and tangles in the dementia of Alzheimer's disease: correlations using three sets of neuropathological criteria. *Dementia* 1995;6:21–31.
12. DeKosky ST, Scheff SW, Styren SD. Structural correlates of cognition in dementia: quantification and assessment of synapse change. *Neurodegeneration* 1996;5:417–421.
13. Lassmann H, Fischer P, Jellinger K. Synaptic pathology of Alzheimer's disease. *Ann NY Acad Sci* 1993;695:59–64.
14. Scheff SW, DeKosky ST, Price DA. Quantitative assessment of cortical synaptic density in Alzheimer's disease. *Neurobiol Aging* 1990;11:29–37.
15. Samuel W, Terry RD, DeTeresa R, et al. Clinical correlates of cortical and nucleus basalis pathology in Alzheimer dementia. *Arch Neurol* 1994;51:772–778.
16. Masliah E, Miller A, Terry RD. The synaptic organization of the neocortex in Alzheimer's disease. *Med Hypotheses* 1993;41:334–340.
17. Wisniewski K, Jervis GA, Moretz RC, et al. Alzheimer neurofibrillary tangles in diseases other than senile and presenile dementia. *Ann Neurol* 1979;5:288–294.
18. Selkoe DJ. Normal and abnormal biology of the B-amyloid precursor protein. *Annu Rev Neurosci* 1994;17:489–517.
19. Vassar R, Bennett BD, Babu-Khan S, et al. β -Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* 1999;286:735–741.
20. Sinha S, Anderson JP, Barbour R, et al. Purification and cloning of amyloid precursor protein beta-secretase from human brain. *Nature* 1999;402:537–540.
21. Yan R, Bienkowski MJ, Shuck ME, et al. Membrane-anchored aspartyl protease with Alzheimer's disease beta-secretase activity. *Nature* 1999;402:533–537.
22. Wolfe MS, Xia W, Ostaszewski BL, et al. Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity. *Nature* 1999;398:513–517.
23. Hutton M, Perez-tur J, Hardy J. Genetics of Alzheimer's disease. *Essays Biochem* 1998;33:117–131.
24. Selkoe DJ. Alzheimer's disease: genotypes, phenotype, and treatment. *Science* 1997;275:630–631.
25. Price DL, Sisodia SS. Mutant genes in familial Alzheimer's disease and transgenic models. *Annu Rev Neurosci* 1998;21:479–505.
26. Erlinge D, Edvinsson L, Brunkwall J, et al. Human neuropeptide Y Y1 receptor antisense oligodeoxynucleotide specifically inhibits neuropeptide Y-evoked vasoconstriction. *Eur J Pharmacol* 1993;240:77–80.
27. Hsiao K, Chapman P, Nilsen S, et al. Correlative memory deficits, A β elevation, and amyloid plaques in transgenic mice. *Science* 1996;274:99–102.
28. Haroutunian V, Perl DP, Purohit DP, et al. Regional distribution of neuritic plaques in nondemented elderly and cases of very mild Alzheimer's disease. *Arch Neurol* 1998;55:1185–1191.
29. Näslund J, Haroutunian V, Mohs R, et al. Elevated amyloid β -peptides in brain: correlation with cognitive decline. *JAMA* 2000;283:1571–1577.
30. Berg L, McKeel DW Jr, Miller JP, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease:

- relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch Neurol* 1998;55:326–335.
31. Morris JC, Storandt M, McKeel DW Jr, et al. Cerebral amyloid deposition and diffuse plaques in “normal” aging: evidence for presymptomatic and very mild Alzheimer’s disease. *Neurology* 1996;46:707–719.
 32. Morris JC, McKeel DW Jr, Storandt M, et al. Very mild Alzheimer’s disease: informant-based clinical, psychometric, and pathologic distinction from normal aging. *Neurology* 1991;41:469–478.
 33. Jicha GA, Berenfeld B, Davies P. Sequence requirements for formation of conformational variants of tau similar to those found in Alzheimer’s disease. *J Neurosci Res* 1999;55:713–723.
 34. Jicha GA, Lane E, Vincent I, et al. A conformation- and phosphorylation-dependent antibody recognizing the paired helical filaments of Alzheimer’s disease. *J Neurochem* 1997;69:2087–2095.
 35. Holzer M, Holzapfel HP, Zedlick D, et al. Abnormally phosphorylated tau protein in Alzheimer’s disease: heterogeneity of individual regional distribution and relationship to clinical severity. *Neuroscience* 1994;63:499–516.
 36. Mandelkow EM, Mandelkow E. Tau as a marker for Alzheimer’s disease. *Trends Biochem Sci* 1993;18:480–483.
 37. Braak H, Braak E. Evolution of the neuropathology of Alzheimer’s disease. *Acta Neurol Scand Suppl* 1996;165:3–12.
 38. Braak E, Braak H, Mandelkow EM. A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. *Acta Neuropathol (Berl)* 1994;87:554–567.
 39. Haroutunian V, Purohit DP, Perl DP, et al. Neurofibrillary tangles in nondemented elderly and very mild Alzheimer’s disease. *Arch Neurol* 1999;57:713–718.
 40. Zubenko G, Henderson R, Stiffler J, et al. Association of the APOE ϵ 4 allele with clinical subtypes of late depression. *Biol Psychiatry* 1996;40:1008–1016.
 41. Gsell W, Strein I, Riederer P. The neurochemistry of Alzheimer type, vascular type and mixed type dementias compared. *J Neural Transm Suppl* 1996;47:73–101.
 42. Nemeroff CB, Bissette G, Slotkin TA, et al. Recent advances in the neurochemical pathology of Alzheimer’s disease: studies of neuropeptides, cholinergic function and Alzheimer’s disease-associated protein. *Ann NY Acad Sci* 1991;640:193–196.
 43. Bierer LM, Haroutunian V, Gabriel S, et al. Neurochemical correlates of dementia severity in Alzheimer’s disease: relative importance of the cholinergic deficits. *J Neurochem* 1995;64:749–760.
 44. Perry EK, Tomlinson BE, Blessed G, et al. Neuropathological and biochemical observations on the noradrenergic system in Alzheimer’s disease. *J Neurol Sci* 1981;51:279–337.
 45. Davies P, Maloney AJF. Selective loss of central cholinergic neurons in Alzheimer’s disease. *Lancet* 1976;2:1403.
 46. Perry EK, Perry RH, Blessed G, et al. Necropsy evidence of central cholinergic deficits in senile dementia. *Lancet* 1977;1:189.
 47. Bissette G, Seidler FJ, Nemeroff CB, et al. High affinity choline transporter status in Alzheimer’s disease tissue from rapid autopsy. *Ann NY Acad Sci* 1996;777:197–204.
 48. Haroutunian V, Santucci AC. Pharmacological animal models of dementia. In: Charney DS, Nestler EJ, Bunney BS, eds. *Neurobiological foundations of mental illness*. New York: Oxford University Press, 1999:669–678.
 49. Davis KL, Thal LT, Gamzu ER, et al. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer’s disease. *N Engl J Med* 1992;327:1253–1259.
 50. DeKosky ST, Harbaugh RE, Schmitt FA, et al. Cortical biopsy in Alzheimer’s disease: diagnostic accuracy and neurochemical, neuropathological, and cognitive correlations. Intraventricular Bethanechol Study Group. *Ann Neurol* 1992;32:625–632.
 51. Bowen DM, Benton JS, Spillane JA, et al. Choline acetyltransferase activity and histopathology of frontal neocortex from biopsies of demented patients. *J Neurol Sci* 1982;57:191–202.
 52. Martin EM, Wilson RS, Penn RS, et al. Cortical biopsy results in Alzheimer’s disease: correlation with cognitive deficits. *Neurology* 1987;37:1201–1204.
 53. Perry EK, Blessed G, Tomlinson BE, et al. Neurochemical activities in human temporal lobe related to aging and Alzheimer-type changes. *Neurobiol Aging* 1981;2:251–256.
 54. Davis KL, Mohs RC, Marin DB, et al. Cholinergic markers are not decreased in early Alzheimer’s disease. *JAMA* 1999;281:1401–1406.
 55. Davies P, Katzman R, Terry RD. Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer’s disease Alzheimer’s senile dementia. *Nature* 1980;288:279–280.
 56. Bissette G. Neuropeptides and Alzheimer’s disease pathology. In: Beckwith BE, Saria A, Chronwall BM, et al., eds. *Neuropeptides in development and aging*. New York: New York Academy of Sciences, 1997:17–29.
 57. De Souza EB, Whitehouse PJ, Price DL, et al. Abnormalities in corticotropin-releasing hormone (CRH) in Alzheimer’s disease and other human disorders. *Ann NY Acad Sci* 1987;512:237–247.
 58. Gabriel SM, Bierer LM, Haroutunian V, et al. Widespread deficits in somatostatin but not neuropeptide-Y concentrations in Alzheimer’s disease cerebral cortex. *Neurosci Lett* 1993;155:116–120.
 59. Perry RH, Perry EK, Smith CJ, et al. Cortical neuropathological and neurochemical substrates of Alzheimer’s and Parkinson’s diseases. *J Neural Transm Suppl* 1987;24:131–136.
 60. De Souza EB, Whitehouse PJ, Kuhar MJ, et al. Reciprocal changes in corticotropin-releasing factor (CRF)-like immunoreactivity and CRF receptors in cerebral cortex of Alzheimer’s disease. *Nature* 1986;319:593–595.
 61. Bissette G, Cook L, Smith W, et al. Regional neuropeptide pathology in Alzheimer’s disease: corticotropin-releasing factor and somatostatin. *J Alzheimer Dis* 1998;1:1–15.
 62. Pomara N, Singh RR, Deptula D, et al. CSF corticotropin-releasing factor (CRF) in Alzheimer’s disease: its relationship to severity of dementia and monoamine metabolites. *Biol Psychiatry* 1989;26:500–504.
 63. Molchan SE, Hill JL, Martinez RA, et al. CSF somatostatin in Alzheimer’s disease and major depression: relationship to hypothalamic-pituitary-adrenal axis and clinical measures. *Psychoneuroendocrinology* 1993;18:509–519.
 64. Mouradian MM, Farah JM Jr, Mohr E, et al. Spinal fluid CRF reduction in Alzheimer’s disease. *Neuropeptides* 1986;8:393–400.
 65. Davis KL, Mohs RC, Marin DB, et al. Neuropeptide abnormalities in patients with early Alzheimer’s disease. *Arch Gen Psychiatry* 1999;56:981–987.
 66. McGeer PL, McGeer EG. Mechanisms of cell death in Alzheimer disease: immunopathology. *J Neural Transm Suppl* 1998;54:159–166.
 67. Aisen PS. Inflammation and Alzheimer’s disease: mechanisms and therapeutic strategies. *Gerontology* 1997;43:143–149.
 68. Rogers J. Inflammation as a pathogenic mechanism in Alzheimer’s disease. *Arzneimittelforschung* 1995;45:439–442.
 69. Pasinetti GM, Aisen PS. Cyclooxygenase-2 expression is increased in frontal cortex of Alzheimer’s disease brain. *Neuroscience* 1998;87:319–324.
 70. Johnson SA, Lampert-Etchells M, Pasinetti GM, et al. Complement mRNA in the mammalian brain: responses to Alzheimer’s

- disease and experimental brain lesioning. *Neurobiol Aging* 1992;13:641–648.
71. Pasinetti GM. Inflammatory mechanisms in neurodegeneration and Alzheimer's disease: the role of the complement system. *Neurobiol Aging* 1996;17:707–716.
 72. McGeer PL, McGeer EG. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res Brain Res Rev* 1995;21:195–218.
 73. Luterman JD, Haroutunian V, Yemul S, et al. Cytokine gene expression as a function of the clinical progression of Alzheimer disease dementia. *Arch Neurol* 2000;57:1153–1160.
 74. Gearing J, Mirra SS, Hedreen J, et al. CERAD. X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. *Neurology* 1995;45:461–466.
 75. Thal LJ, Grundman M, Klauber MR. Dementia: characteristics of a referral population and factors associated with progression. *Neurology* 1988;38:1083–1090.
 76. Small GW, Rabins PV, Barry PP, et al. Diagnosis and treatment of Alzheimer's disease and related disorders. *JAMA* 1997;278:1363–1371.
 77. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology* 1998;51:728–733.
 78. Ho LX, Keller DM. Prevalence of AD among whites: a summary by levels of severity. *Neurology* 2000;55:198–204.
 79. Stern Y, Gurland B, Tatemichi TK, et al. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994;271:1004–1010.
 80. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele 4 with late-onset familial Alzheimer disease. *Neurology* 1993;43:1467–1472.
 81. Meyers RH, Schaefer EJ, Wilson PWF, et al. Apolipoprotein E ϵ 4 association with dementia in a population-based study: the Framingham Study. *Neurology* 1996;46:673–677.
 82. Jacobs DM, Sano M, Dooneief G, et al. Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology* 1995;45:957–962.
 83. Masur DM, Sliwinski M, Lipton RB, et al. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology* 1994;44:1427–1432.
 84. Petersen RC, Smith GE, Ivnik RJ, et al. Memory function in very early Alzheimer's disease. *Neurology* 1994;44:867–872.
 85. 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.
 86. Blacker D, Haines JL, Rodes L, et al. ApoE-4 and age at onset of Alzheimer's disease. *Neurology* 1997;48:139–147.
 87. Welsh KA, Butter N, Hughes J, et al. Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. *Arch Neurol* 1991;48:278–281.
 88. Morris JC, Edland S, Clark C, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. *Neurology* 1993;43:2457–2465.
 89. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
 90. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968;114:797–811.
 91. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984;141:1356–1364.
 92. Rogers SL, Doody RS, Mohs RC, et al. Donepezil improves cognition and global function in Alzheimer's disease: a 15-week, double-blind, placebo-controlled study. *Arch Intern Med* 1998;158:1021–1031.
 93. Stern RG, Mohs RC, Bierer LM, et al. Deterioration on the Blessed test in Alzheimer's disease: longitudinal data and their implications for clinical trials and identification of subgroups. *Psychiatry Res* 1992;42:101–110.
 94. Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate and predictors of cognitive deterioration. *Am J Psychiatry* 1994;151:390–396.
 95. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:2308–2314.
 96. Mohs RC, Ferris SH. Measuring response to treatment in Alzheimer's disease: what constitutes meaningful change? *Int J Geriatr Psychopharmacol* 1998;1:S7–S14.
 97. Marin DB, Green CR, Schmeidler J, et al. Noncognitive disturbances in Alzheimer's disease: frequency, longitudinal course and relationship to cognitive symptoms. *J Am Geriatr Soc* 1997;45:1331–1338.
 98. McKhann G, Drachman DA, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944.
 99. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–186.
 100. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzheimer Dis Assoc Disord* 1997;11:S33–S39.
 101. Green CR, Mohs RC, Schmeidler J, et al. Functional decline in Alzheimer's disease: a longitudinal study. *J Am Geriatr Soc* 1993;41:654–661.
 102. Green CR, Marin DB, Mohs RC, et al. The impact of behavioral impairment on functional ability in Alzheimer's disease. *Int J Geriatr Psychiatry* 1999;14:307–316.

