# Preface

As the population ages, an increasing number of individuals are at risk for degenerative diseases such as Alzheimer's disease (AD). *Early Diagnosis of Alzheimer's Disease* has been written out of the conviction that without an understanding of the complex issues surrounding the search for early markers for Alzheimer's disease, the prospects for early diagnosis and, consequently, the development of new interventions for the disease will, at best, be delayed. In the past few years, we have seen a proliferation of research on methods to detect Alzheimer's disease early in its course. It is an excellent time to take stock of the progress of this rapidly expanding field.

The chapters in *Early Diagnosis of Alzheimer's Disease* review the most promising approaches in current research on early diagnostic markers for AD. These approaches include the elucidation of changes in the brain as seen in structural and functional neuroimaging, characteristic patterns of cognitive decline as documented by sensitive neuropsychological tests, various genetic markers, and a wide array of biological assays. We have placed these different approaches to early diagnosis within a broader context by also reviewing current clinical practice in diagnosing AD, major theories about its pathophysiology, and the therapeutic and ethical implications of early diagnosis. Each of the areas explored in *Early Diagnosis of Alzheimer's Disease* holds promise for contributing to the development of strategies for meeting the diagnostic and therapeutic challenge posed by AD.

*Early Diagnosis of Alzheimer's Disease* is addressed to a broad audience within the biomedical research and clinical communities. It should be of interest to clinicians who endeavor to care for an aging population, researchers working in the area of new therapeutic approaches to the disease, and policymakers who are concerned about the implications surrounding early diagnosis and the delivery of health care. Although the work gathered here provides a timely summary of different approaches for the early diagnosis of AD, we hope it will make a more lasting contribution in setting a framework for future research and critical thinking on the many issues surrounding early diagnosis. We are grateful to our fellow authors who have contributed their time and expertise to this work. Such a cooperative effort by many scholars from a variety of disciplines serves as a model for how important questions concerning diagnosis and therapy will need to be pursued to find adequate solutions to the puzzle of AD.

We thank the staff at Humana Press for their patience and care in the production of this volume. We appreciate the effort of Barbara Vericker during the planning and execution of this work. Her talents have added immeasurably to its successful completion.

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# 2

# Current Approaches to the Clinical Diagnosis of Alzheimer's Disease

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## Introduction

Assessing the value of new diagnostic approaches to Alzheimer's disease (AD) requires an appreciation of the "standard" clinical diagnostic evaluation. In reality, there is no single, universally accepted clinical approach to the evaluation of demented patients. The workup is likely to vary from setting to setting. Different approaches may be found, for example, among primary care physicians, clinical neurologists in the community, and dementia researchers in academic centers. With the growth of managed care programs, more explicit standards may be established, perhaps with an increased emphasis on containing costs.

Two antithetical attitudes about diagnosis of dementia are common even within the medical community, each with damaging consequences. One is that changes in cognition and behavior seen in elderly individuals are simply a reflection of the normal aging process and thus can be readily dismissed. The second is that all disruptive cognitive decline in the elderly is due to Alzheimer's disease. The terms dementia and Alzheimer's disease often are used interchangeably. Either of these attitudes can lead to the unfortunate view that there is no need to make an effort to accurately diagnose dementia. Clearly, accuracy of diagnosis will become increasingly important as more treatments become available. Even now, accuracy of diagnosis remains an important goal. Perhaps most significantly, such efforts can help identify potentially reversible or treatable conditions that have contributed to cognitive decline and dementia. Accuracy of diagnosis can provide important prognostic information to families that allow for generating appropriate expectations

and plans for the patient's future needs. In addition, it can allow family members to consider the implications that a particular diagnosis might have for them in terms of their own future. Finally, before the establishment of clear in vivo markers for Alzheimer's disease, trials to assess the efficacy of new medications for AD depend on the accurate clinical diagnosis to identify patients who most likely are suffering from Alzheimer's disease. Including misdiagnosed patients without Alzheimer's disease in such trials is likely to dilute the results of potentially efficacious treatments *(1)*.

In the absence of definitive diagnostic markers for Alzheimer's and other dementing illnesses, clinicians and researchers have turned to provisional strategies for trying to accurately assess a patient's clinical status and diagnosis. The need for developing rational guidelines to assist in the diagnosis of AD has become more apparent with the growing magnitude of the problem of dementia. Alzheimer's disease is the major cause of dementia in the United States, accounting for 55% to 70% of cases *(2–4)*. This disease alone constitutes a significant and increasing health care problem. Prevalence of AD has risen steadily as the average age of the population has increased. It is estimated that up to 10% of Americans 65 and older suffer from the disease *(5,6)*. For the population of 85 and older, estimates of prevalence have been as high as 47% *(7)*. As many as four million Americans may suffer from AD, with the cost in excess of 100 billion dollars per year *(8)*.

This chapter emphasizes practices that have been codified over the last 10–15 years by several prominent research and clinical groups. Many of these standards were originally developed to establish diagnostic criteria for research purposes such as the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM) *(9),* the task force report of the National Institutes of Neurologic and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS–ADRDA) *(10),* and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) *(11–13)* but are now used as guidelines in clinical practice. Others *(14–17)* have been developed to help direct the practicing clinician (e.g., Quality Standards Subcommittee of the American Academy of Neurology). The extent to which practitioners actually follow these guidelines, however, has not been clearly established. Thus, this chapter provides information about "recommended" clinical workups, not about how often they are actualized in the community.

## Initiation of a Dementia Evaluation

Evaluations for dementia are initiated under different circumstances. Most often, family members bring in a loved one because they are concerned about a decline in his/her cognitive or behavioral status. Patients who often lack insight

due to their central nervous system (CNS) disease (or psychological defenses), are unlikely to recognize the need for such an evaluation. Other patients may accept some of the observations of decline made by their loved ones, but downplay their implications. Increasingly, patients themselves seem to be sharing concerns with their physicians about problems with forgetfulness, word-finding difficulties, or slowness in retrieving names. Some of these patients will be in the early stages of a dementing illness. Others may be particularly sensitive to the cognitive changes that are associated with "normal" aging or be suffering from depression *(18,19)*. Requests for evaluation may become increasingly common as information about dementia and Alzheimer's disease inundates the popular press. A third pathway for initiating an evaluation is established when interactions between a patient and medical staff raise concerns about the patient's mental state or ability to manage his or her affairs independently.

Workup of a potentially demented patient is a multidimensional process with two major branching points (American Academy of Neurology practice parameters algorithm) (Fig. 1). The first major step involves establishing whether or not an individual fits criteria for being clinically demented. The second major step occurs after establishing a diagnosis of dementia and involves a workup to evaluate possible underlying conditions that fall within the differential diagnosis. Establishing a diagnosis of dementia relies principally on a detailed history and mental state assessment. Identifying the most likely underlying causes of dementia relies on recognizing the salient patterns of cognitive decline as revealed by the history and mental state examination and obtaining appropriate diagnostic studies that look for potential contributions to the deterioration in the patient's cognitive or behavioral status.

## Diagnostic Criteria

The defining criteria for dementia vary *(9,10,16,17)*. Our working definition is as follows: Dementia is a progressive, but not necessarily irreversible, decline in cognitive or behavioral functioning that interferes with daily living activities that are appropriate for one's age and background and is not simply due to a delirium, confusional state, or related alteration in sensorium. Both DSM-IV and NINCDS-ADRDA diagnostic criteria for dementia require a decline in memory and other cognitive processes such as language, visual-spatial abilities, or executive functions. DSM-IV criteria explicitly states that such cognitive deficits must "cause significant impairment in social or occupational functioning (e.g., going to school, working, shopping, dressing, bathing, handling finances, and other activities of daily living) and must represent a decline from a previous level of functioning" *(9)*. This criterion is not explicitly included in the NINCDS-ADRDA formula (Table 1). In both
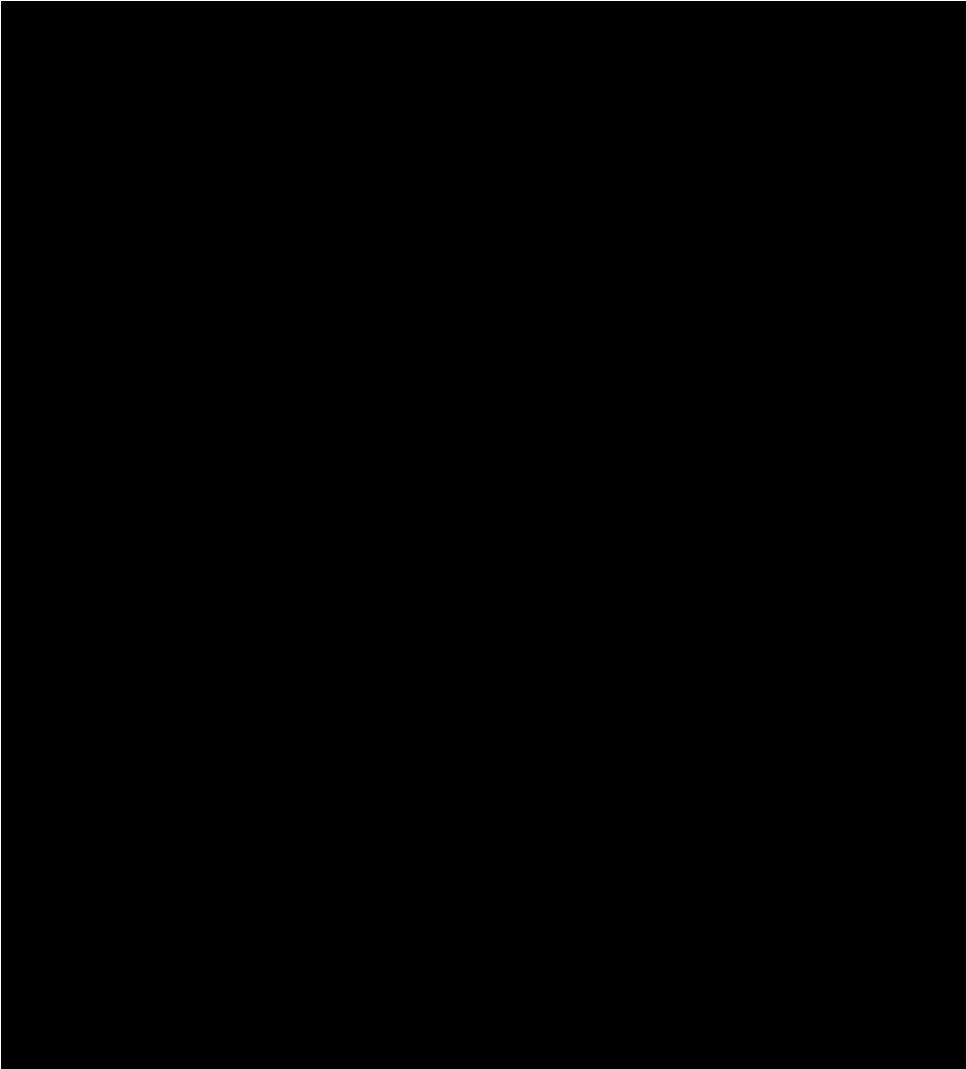
**Fig. 1.** Proposed algorithm for dementia diagnosis and workup. *Suspected and worrisome history without obvious abnormalities on office mental state testing. **Some physicians will work up patients who show no functional decline without doing neuro-psychological testing. (Reprinted with permission from *Neurology* 1995; 45:212.)

schemes, dementia cannot be appropriately diagnosed in the context of an altered sensorium such as delirium or confusional state. It is also important to point out that the diagnosis of dementia is a clinical one. It reflects impairments in neuropsychological and functional status. As such, the diagnosis of dementia cannot be made by a pathologist, neuroradiologist, or blood test.
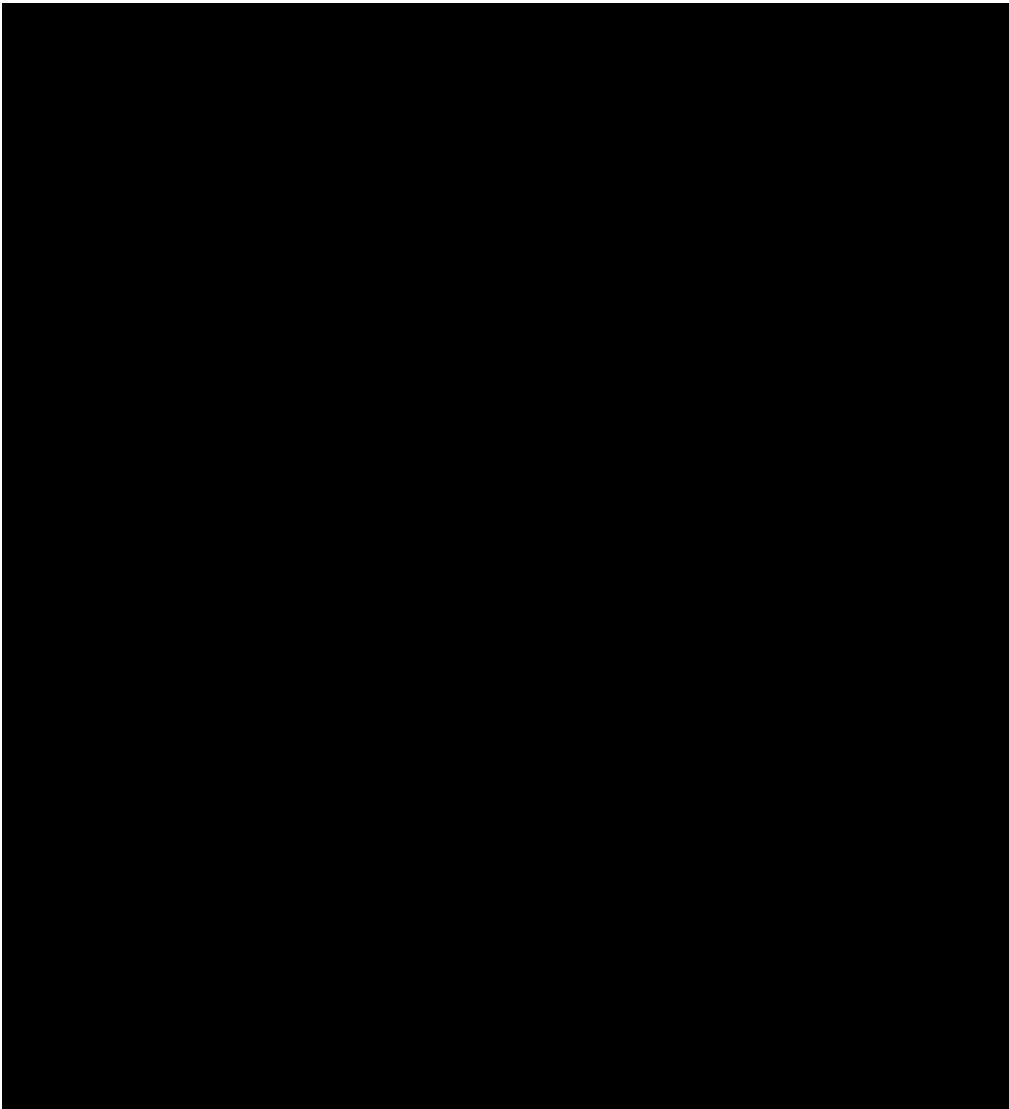
## Components of a Dementia Evaluation

### *History: Changes in Cognitive and Functional Status*

Perhaps the most crucial aspect of establishing the diagnosis of dementia in a patient is obtaining a detailed history. Most often this requires a reliable informant, such as a family member or friend. The patient's dementing condition often prevents the individual from providing an accurate picture of his or her personal history. The clinician needs to inquire about the patient's premorbid, baseline cognitive and behavioral status, education, and highest level of personal achievements. For example, the manifestations of a decline in cog-

nitive and functional status will be very different for a person who was highly educated and held positions of great responsibility compared to a person who at baseline had borderline intellectual capacities, a grade-school education, and worked menial jobs. One inquires about changes in mental abilities that can present as forgetfulness, episodes of getting lost, word-finding difficulties, paraphasic errors, and a tendency for the patient to repeat herself. One asks about changes in personality, mood, and behavior, including evidence of sadness, withdrawal, apathy, inappropriateness, impulsivity, irritability, suspiciousness, and altered appetitive behaviors. Is there evidence to suggest hallucinations, illusions, misperceptions, or delusions (e.g., that others are stealing things from the patient or that one's spouse is unfaithful)?

Inquiries should be made of observed changes in functional status and daily living activities including job performance if the patient is still working, household responsibilities and chores, family finances, self-care, personal hygiene, and episodes of incontinence. Informants should also be asked if they have noted changes in motor functioning such as focal weakness, tremor, stiffness, or gait disturbance. Establishing the onset and temporal pace of changes in mental state is helpful in elucidating potential underlying disease processes. When were the cognitive problems first noted? What were their initial features? Have the changes been insidiously progressive (suggestive of a degenerative disease) or stepwise (more suggestive of vascular insults)? Has the decline been rapid (suggestive of possible infectious process or toxic metabolic state) or more chronic in nature?

### Past Medical History

Past medical history and ongoing medical conditions also may provide clues about processes contributing to a decline in cognitive functioning. Specifically, the clinician wants to inquire about a history of cerebrovascular disease, systemic illness, and risk factors for infections. Also pertinent are current and past medication use, a history of alcohol or substance abuse, major head trauma, depression or other psychiatric illness, poor nutritional status, and potential exposure to toxins. Finally, one wants to identify if there is a family history of dementing illness or other diseases that can affect the central nervous system. If so, what was the age of onset of the dementia in the family member, the clinical characteristics, and was there an autopsy that confirmed the suspected underlying pathology?

### Mental State Evaluation

A mental state examination is an essential feature of a dementia assessment. This may be the most variable aspect of the evaluation among clinicians. There is no consensus among neurologists, psychiatrists, or primary
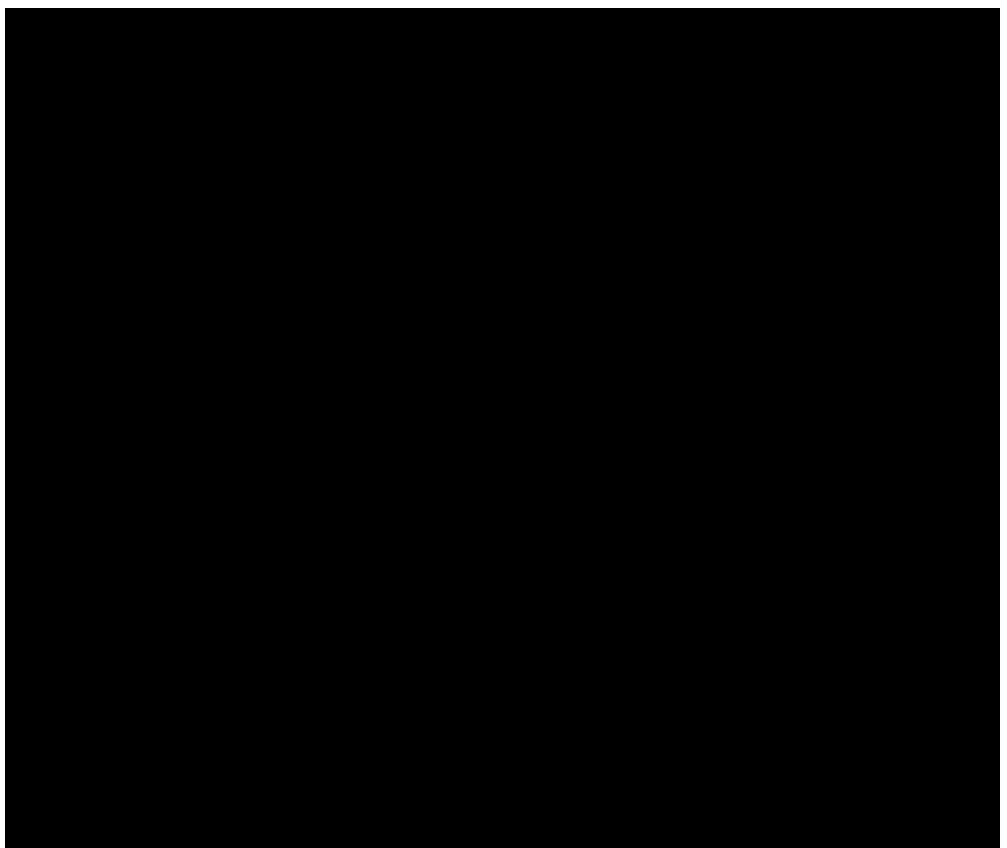
care physicians of the "best" mental state screening examination or testing strategy to use. Most would agree on the need to assess the following domains: orientation, attention, recent memory, long-term memory, language, praxis, visual-spatial functions and executive functions (insight, judgment, planfulness). It is important for clinicians to have a means of estimating whether a patient's performance falls within age-appropriate norms. There are several standard mental state screening tools that clinicians use, including the Mini Mental State Exam (MMSE) *(20)* and the Blessed Dementia Scale [Information–Memory–Concentration subset (BDS-IMC)] *(21)* (Table 2A,B). Such instruments have certain clear advantages including being brief, standardized, and reasonably well-normed. In addition, there are published reports of cutoff values that are adjusted for various ages and educational backgrounds *(22,23)*. Such tests can serve as a screening device for dementia or cognitive impairment and provide a measure of intellectual decline over time *(24–27)*. However, they are often insensitive to early, subtle cognitive impairments, especially in well-educated, highly intelligent individuals *(28)*. In addition, they are insensitive to late changes in dementia severity *(29)*. Finally, they serve as global screening devices and provide very limited information about damage to specific neurocognitive systems and their associated neuroanatomical networks. Such patterns of cognitive impairment often provide important information for identifying the most likely underlying disease processes *(30–32)* (see Chapter 8). A very poor performance on a mental state screening test certainly can help identify patients suffering from a dementing illness. If there is a discrepancy between an informant's observations of cognitive and behavioral functioning and the patient's performance on mental state tests, it suggests the need for close follow-up and further investigation with more extensive neuropsychological testing.

### *Sensorimotor Examination*

The sensorimotor neurological examination does not contribute to making a diagnosis of dementia per se. However, the pattern of neurological abnormalities often point to likely underlying diseases that may be contributing to the dementing process. For example, a clinician should look for evidence of upper motor neuron signs (e.g., hemiparesis, asymmetric deep tendon reflexes, extensor plantar responses) that would suggest the possibility of stroke or structural lesion. Extrapyramidal signs would raise the question of Parkinson's disease, progressive supranuclear palsy, or Lewy body dementia. Abnormalities of gait may be associated with cerebrovascular disease,
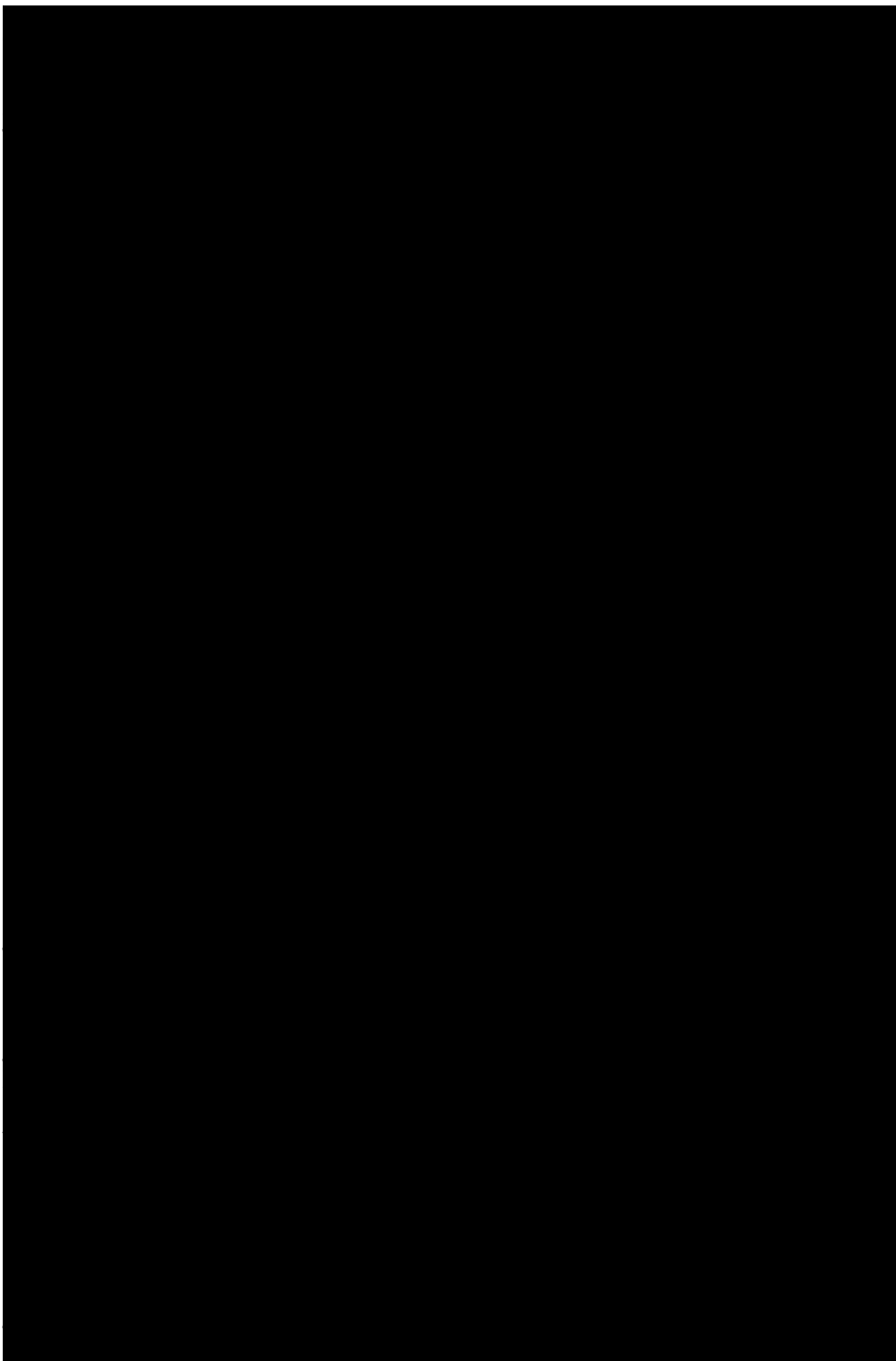
Parkinson's disease, and normal pressure hydrocephalus. Dysarthria would alert the clinician to possible extrapyramidal disorders, bilateral strokes, demyelinating disease, and motor neuron disease. Sensory abnormalities (e.g., peripheral neuropathy) may be associated with $B_{12}$, other vitamin deficiency states, thyroid disease, or a paraneoplastic syndrome. Cerebellar signs might raise concerns about cerebrovascular disease, spinocerebellar degeneration, a paraneoplastic syndrome, and Creutzfeldt-Jakob disease. In Alzheimer's disease, especially early in its course, the sensorimotor examination tends to be relatively benign. Some researches have pointed out that the presence of extrapyramidal signs in patients with a profile otherwise consistent with Alzheimer's disease suggests a worse prognosis *(33)*. Extrapyramidal signs may indicate the presence of Lewy body variant of AD *(34)*. In general, if a patient with dementia presents with focal or multifocal neurological signs, the clinician should investigate diseases other than AD that may be contributing to the patient's decline in status.

### Laboratory Studies

Laboratory studies help to rule out potentially reversible causes of dementia. Initially, the literature suggested that reversible dementias occurred in 10–15% of cases; however, recent reports have pointed to a lower frequency *(35–38)*. The practice parameters of the American Academy of Neurology *(14)* recommend that a workup include the following: complete blood count, electrolytes, calcium, glucose, BUN, creatinine, liver function tests, thyroid function tests, $B_{12}$, and syphilis serology. Many would also include a sedimentation rate, urinalysis, and chest radiograph. A patient's history should help guide other tests that may need to be ordered. For example, a patient with a long history of smoking should have a chest radiograph if none has been done recently. Someone with a history of high-risk sexual behaviors or exposure to intravenous drugs should have HIV testing. Patients who may have been exposed to industrial toxins at work should be considered for 24-hour urine collection for heavy metals. Currently, acquisition of ApoE genotyping is not recommended for routine evaluations *(39–43)* and is discussed more thoroughly in Chapter 5.

### Neuroimaging

Traditionally, neuroimaging [computed tomography (CT) scan or magnetic resonance imaging (MRI)] has been used to rule out potential structural abnormalities that may be causing or contributing to a decline in cognitive functioning. Specifically, the clinician is looking for evidence of tumor, subdural hematoma, hydrocephalus, large and small vessel strokes, and white matter disease. The MRI is much more sensitive than CT in detecting abnormalities in white matter *(44),* although the clinical significance of such white matter changes is often unclear *(45)*. Atrophy is common in degenerative dementias such as Alzheimer's disease. However, such a finding is not diagnostic and cannot clearly distinguish demented patients from those undergoing normal aging *(46)*. Structural lesions, such as tumor, hydrocephalus, or subdural hematomas, are reported to be relatively uncommon in several recent series of patients being evaluated at out-patient dementia clinics *(36,37,47)*. By contrast, Bradshaw and colleagues *(48)* identified structural lesions in almost 10% of patients being evaluated for dementia, including 5% who had no associated focal signs or symptoms. Furthermore, Katzman *(49)* has noted that the incidence of structural lesions tends to be higher in large autopsy series of demented patients than in studies of patients being evaluated by outpatient dementia clinics. He raises the possibility of a selection bias in the outpatient series. Patients with structural lesions may have been identified by CT scan in the community and referred to a

neurosurgeon rather than to a dementia clinic. Many would advocate that obtaining neuroimaging is worth the expense because structural lesions represent potentially treatable entities *(49)*. Others have argued against the routine acquisition of neuroimaging in patients with an insidiously progressive dementia beginning after the age of 60, who lack focal signs or symptoms, seizures or gait disturbance *(37,47)*. In fact, the American Academy of Neurology practice parameters do not designate neuroimaging as "standard procedure" but leaves it up to the judgment of the individual clinician *(14)*.

Recent approaches to identifying patients with Alzheimer's disease using morphometric analysis of temporal lobe structures are discussed in Chapter 6. PET, SPECT, and functional MRI are currently not part of a routine dementia workup. Their potential usefulness is discussed in Chapter 7. In current clinical practice, functional imaging may be particularly helpful in the workup of dementias with atypical presentations. Such studies can support the diagnosis of degenerative diseases that are less common than Alzheimer's disease such as a frontotemporal dementia, which is associated with hypoperfusion in the anterior regions of the brain *(50–52)*.

### Neuropsychological Testing

Formal neuropsychological tests also are not part of the routine workup of patients with possible dementia. Such testing can provide a quantitative assessment of a range of cognitive domains. Establishing a patient's performance during an initial assessment allows for quantitative measurement of decline in cognitive status over time. Progressive impairments of cognitive abilities, especially if they exceed age-matched norms, are very suggestive of an underlying dementing process. Neuropsychological assessment is particularly helpful for a patient whose results on an initial evaluation and mental state screen are ambiguous, and the suspicion of an early dementing process remains. Such assessment can help establish areas of cognitive impairment before decline in functional status that accompanies clinical dementia. As noted, certain patterns of cognitive impairment have implications for which neuroanatomical networks are likely disturbed by the underlying disease process, which in turn have implications about the most likely underlying etiology *(30–32)* (see Chapter 8). For example, patients with probable AD whose pathology often begins in the temporolimbic cortex that subserves memory tend to demonstrate significant impairments in the realm of memory before crossing the "threshold" into a clinical dementia *(53–58)*.

Neuropsychological assessment also can be extremely helpful in patients whose baseline cognitive and educational status was in either the very superior or borderline range. There are strategies for estimating premorbid cogni-

tive abilities against which to compare current intellectual functioning *(59,60)*. Education-adjusted norms are available for some cognitive tests *(61,62)*. Unexpected or excessive scatter in performance on different cognitive tests raises questions about a patient's current intellectual status that would require monitoring. Finally, neuropsychological tests are also particularly helpful in documenting atypical patterns of dementia, in which, for example, memory problems are not the most salient feature.

### CSF Evaluation

Lumbar puncture with cerebrospinal fluid (CSF) analysis is no longer part of the routine evaluation of dementia. This procedure is appropriate if there are concerns about any of the following: CNS infection (e.g., fever, headache), carcinomatous meningitis, reactive syphilis serology, subacute onset, or other atypical presentations of dementia, or if dementia occurs under the age of 50 *(14,63,64)*. In addition, lumbar puncture is indicated when there is evidence that a patient may be suffering from an inflammatory or vasculitic process or when the patient is immunosuppressed. A recent report suggested that the diagnosis of Creutzfeldt-Jakob disease could be confirmed with reasonably high sensitivity and specificity in demented patients without a history of recent infarction or encephalitis who were found to have the protein 14-3-3 in their CSF *(65, 65a, 65b, 65c)*. The potential usefulness of CSF levels of tau protein, β-amyloid, or $\alpha_1$-antichymotrypsin for the diagnosis of Alzheimer's disease are discussed in Chapter 9.

### EEG

An electroencephalogram (EEG) is also not currently part of a standard dementia evaluation. Although the EEG of a demented patient often reveals a slowed background, this pattern lacks specificity. It can also be seen in "normal" aging and be found in a variety of dementing illnesses. Quantitative EEG analysis has pointed to patterns of abnormal electrical activity that are seen more commonly in Alzheimer's disease than normal aging *(66,67)*. However, to date such analyses have not yielded sufficient sensitivity and specificity to justify the routine use of such tests in the diagnostic evaluation of dementia *(68)*. It may turn out that the overlap in findings between AD patients and normal aging controls in quantitative EEG and other tests is largely due to the fact that some of the "normal" subjects had underlying AD pathology that disrupted normal functioning without yet causing a clinical dementia. As with many other techniques, ordering an EEG should be guided by the history and neurological examination. Specifically, an EEG is helpful in evaluating for

possible toxic-metabolic encephalopathy, seizures, encephalitis, or Creutzfeldt-Jakob disease *(69,70)*.

### Cerebral Biopsy

Currently, brain biopsy in patients with dementia is pursued very infrequently. In experienced centers, mortality is probably under 1% and postoperative morbidity is relatively low *(70–72)*. However, most clinicians would not recommend such an invasive procedure unless the results would lead to a change in the therapy or management of the individual patient. Thus, biopsy is considered in cases in which there is a concern about possible atypical infectious, inflammatory, vasculitic, or demyelinating processes. Unfortunately, 20–25% of cerebral biopsies for dementia do not yield a specific diagnosis *(70)*.

## First Major Decision Point: Abnormal Versus Normal Status

The evaluation of dementia can proceed in a relatively orderly fashion. The first major task is to determine if a patient is exhibiting abnormal cognitive abilities and a decline in function. As noted, an appreciation of the patient's baseline mental state and achievements is crucial in making such an assessment. In addition, a clinician needs to be aware of changes associated with normal aging to determine whether a patient exceeds these bounds. On average, many cognitive functions decline in later life, including speed of mental processing and responding, digit span, visual-perceptual abilities, mental flexibility and abstractions *(73–76)*. Acquisition of the new information also is diminished. However, once encoded, there does not tend to be a significant loss of information over time regardless of a patient's level of education *(77)*.

Most importantly, these age-related cognitive changes do not lead to significant interference with the maintenance of an independent and productive life. The mental state screening tests discussed earlier are a means of rapidly assessing a patient's current level of performance and can be compared to established norms. If the patient's performance on mental state examination is borderline or questionable, or if by history the patient appears to be exhibiting a decline in functioning, even with an apparently normal screening mental status examination, the provider should strongly consider formal neuropsychological tests and arrange follow-up in 6 to 12 months to assess whether the decline is progressive.

If there is clear evidence of cognitive impairments, the next task is to determine if the mental state changes reflect a delirium, altered sensorium, or acute confusional state. The salient abnormality in such conditions is inattention, in

which the patient exhibits an inability to maintain a coherent stream of thought or behavior. The most common etiology of an acute confusional state in the elderly is a toxic-metabolic encephalopathy due to side effects from medications, systemic illness, or end organ failure. As noted, a diagnosis of dementia is inappropriate if mental state changes occur in the setting of an acute confusional state. Clinicians need to treat the underlying conditions and reevaluate the patient's mental capacities once the confusional state has resolved. Of particular note, demented individuals are themselves very vulnerable to developing acute confusional states *(78,79)*. They are exquisitely sensitive to a perturbation of their internal or external environments. This condition has been called a "beclouded dementia," indicating that there is a delirium superimposed upon an underlying dementia *(80)*. Such individuals never return to a "normal" cognitive state. Obtaining a careful history regarding the patient's recent "baseline" status (before becoming more acutely confused) can be very informative. Specifically, one wants to know if the change in mental state emerged against a background of a previously well-functioning or cognitively compromised individual.

## Second Major Decision Point: Differential Diagnosis

Once the diagnosis of dementia has been made, the clinician needs to establish the most likely underlying etiology of the condition. Traditionally, this involves trying to "rule out" potentially treatable or reversible etiologies of dementia that may be identified by the workup discussed earlier. Specifically, one aims to exclude encephalopathies due to metabolic problems (e.g., thyroid deficiency) or side effects from medications, CNS infections, vitamin deficiencies, or structural lesions (e.g., hydrocephalus, tumor, subdural hematoma). These conditions tend to account for small percentage of patients presenting with dementia *(36–38)*. When these conditions have been excluded, the two largest remaining disease categories are the degenerative dementias (of which Alzheimer's disease is by far the most common) and vascular dementia.

## Major Patterns of Dementia

Diagnostic accuracy may be improved if the clinician is also attentive to the *pattern* of mental state dysfunction exhibited by a patient, which within the context of the patient's specific history, point to a circumscribed set of disease processes that are most likely to be contributing *(30,31)*. By employing this strategy, the clinician not only attempts to "rule out" certain entities but also to identify clinical patterns with a high likelihood of being associated with specific kinds of underlying pathologies.

### Progressive Amnestic Dementia
### (Probable Alzheimer's Disease)

The most common pattern is a progressive amnestic dementia, in which deterioration in memory functions is the salient feature. The course is insidiously progressive, with memory impairments usually being the initial source of disruption of daily activities. Informants often provide a history of progressive problems with recalling recent events, misplacing objects, repeating questions, becoming disoriented or lost, producing the wrong words, or exhibiting fluent but "empty" speech. Early on, there may be subtle changes in personality in the form of increased disengagement or withdrawal from activities, but grossly inappropriate behaviors are unusual *(81,82)*.
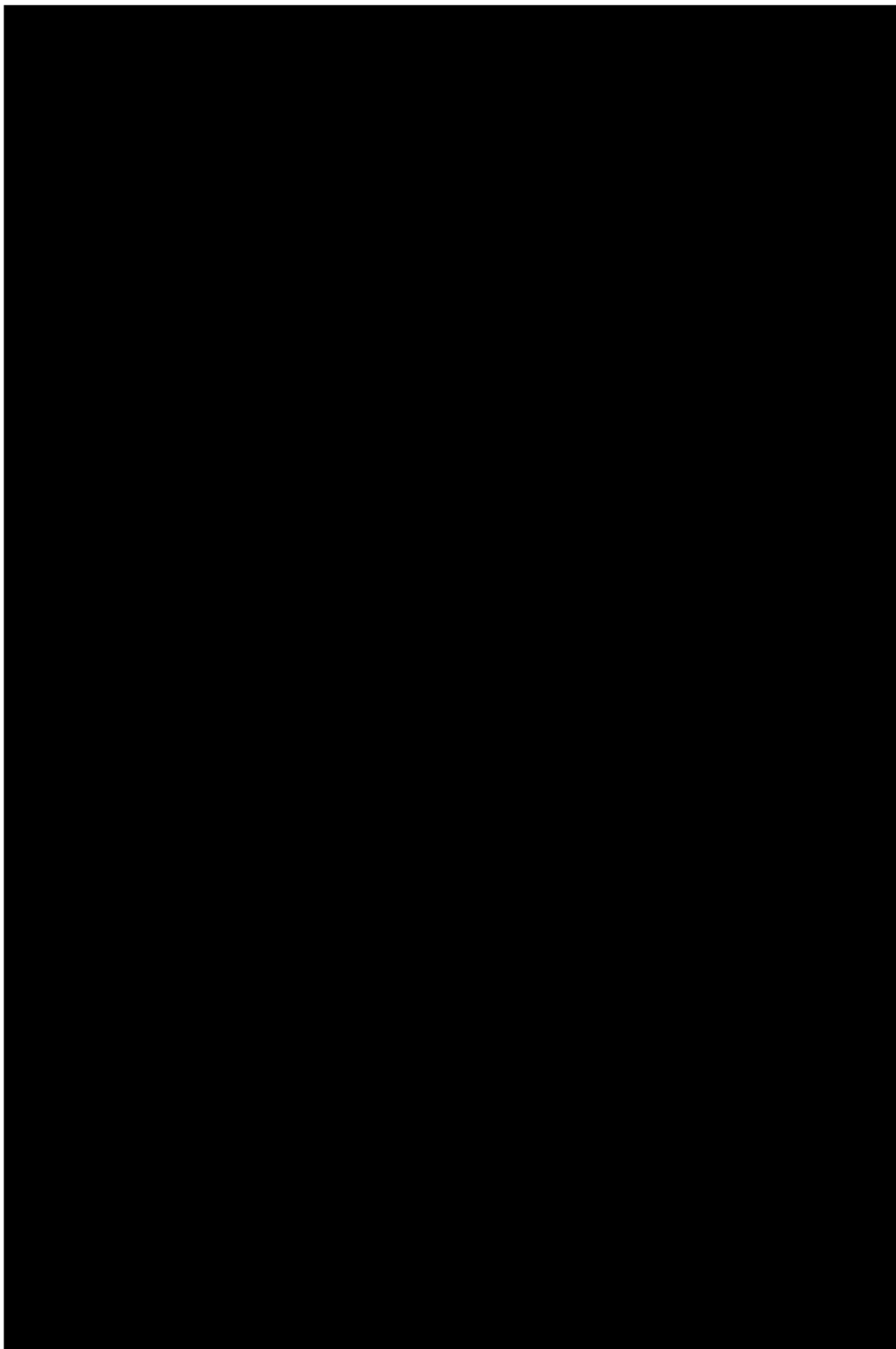
On mental state testing, the dominant problems involve the storage, retention or retrieval components of memory. Language and visuospatial functions also are usually abnormal and over time insight, attention and executive functions deteriorate. Atrophic changes on CT or MRI are most common. When functional imaging is done, the most likely pattern reflects abnormalities in temporoparietal regions bilaterally.
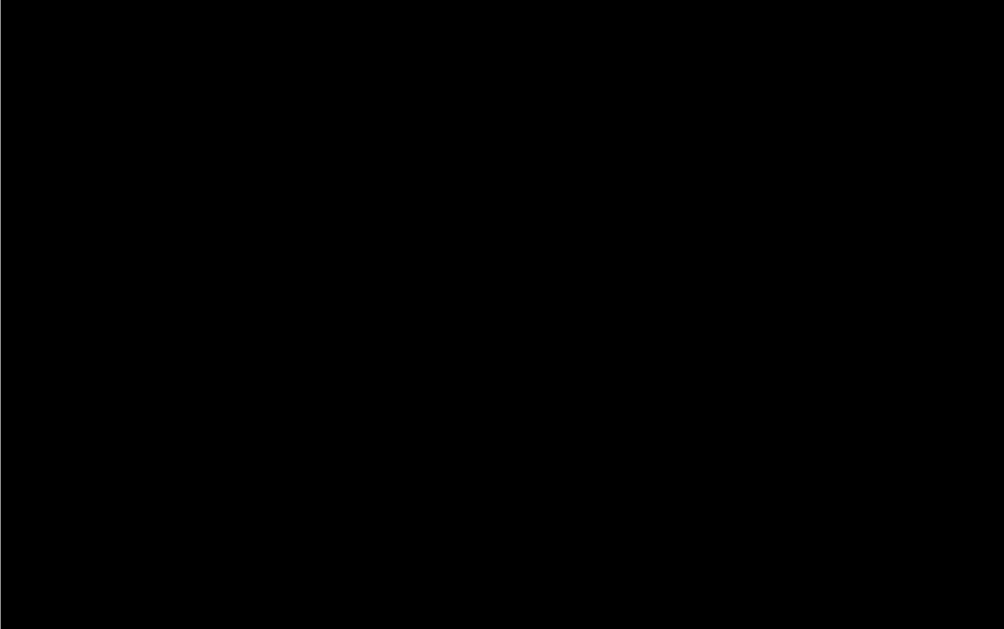
This dementia profile is the most frequent one seen in the elderly and is most often associated with the plaque and tangle pathology of Alzheimer's disease. The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS–ADRA) *(10)* has codified the clinical criteria associated with the high likelihood of Alzheimer's pathology (Table 3). The major elements defining "probable Alzheimer's disease" (PrAD) include:

1. Presence of dementia
2. Progressive worsening of memory and other cognitive functions
3. Deficits in two or more areas of cognition
4. No disturbance of consciousness
5. Age of onset between 40 and 90
6. Absence of systemic or CNS disorders that could account for the dementia

The diagnosis of "possible Alzheimer's disease" is appropriate when a patient exhibits an atypical presentation or clinical course, progressive decline of a single cognitive deficit, or in the presence of a second systemic or brain disorder sufficient to produce the dementia that is not considered to be the cause of the dementia. "Definite Alzheimer's disease" can only be diagnosed when in life the patient had met criteria for probable Alzheimer's disease and at autopsy (or by biopsy) there is appropriate histopathological evidence of Alzheimer's pathology. DSM-IV criteria for "dementia of the Alzheimer's type" (DAT) are simi-

lar to the NINCDS–ADRDA criteria. First, one needs to ensure that a patient fits the criteria for dementia as noted on Table 1. Furthermore, according to DSM-IV, the course of DAT is characterized by gradual onset, continuing cognitive decline, and is not due to other CNS or systemic conditions that cause progressive deficits in memory and cognition (Table 4).

Other degenerative diseases that have been associated with a progressive amnestic dementia include diffuse Lewy body disease, Pick's disease, and focal neuronal atrophy *(34,83–85)*. However, these pathological processes are much less common than Alzheimer's disease. In addition, there are a number of nondegenerative processes that have been associated with the "amnestic syndrome." Most often, however, these are not progressive processes. They include anoxia, carbon monoxide poisoning, posterior cerebral artery strokes, anterior cerebral artery aneurysm with bleed or surgery, Korsakoff's syndrome, head trauma, and herpes encephalitis.

### Dementias With a Prominent Dysexecutive Syndrome

A second major dementia pattern involves patients who exhibit salient changes in personality and behavior, accompanied by compromised attention, motivation, judgment, insight, and other "executive" functions. This clinical entity has been given several names including frontotemporal dementia (FTD), dementia of the frontal lobe type, and comportmental dementia *(30,50,86–88)*.
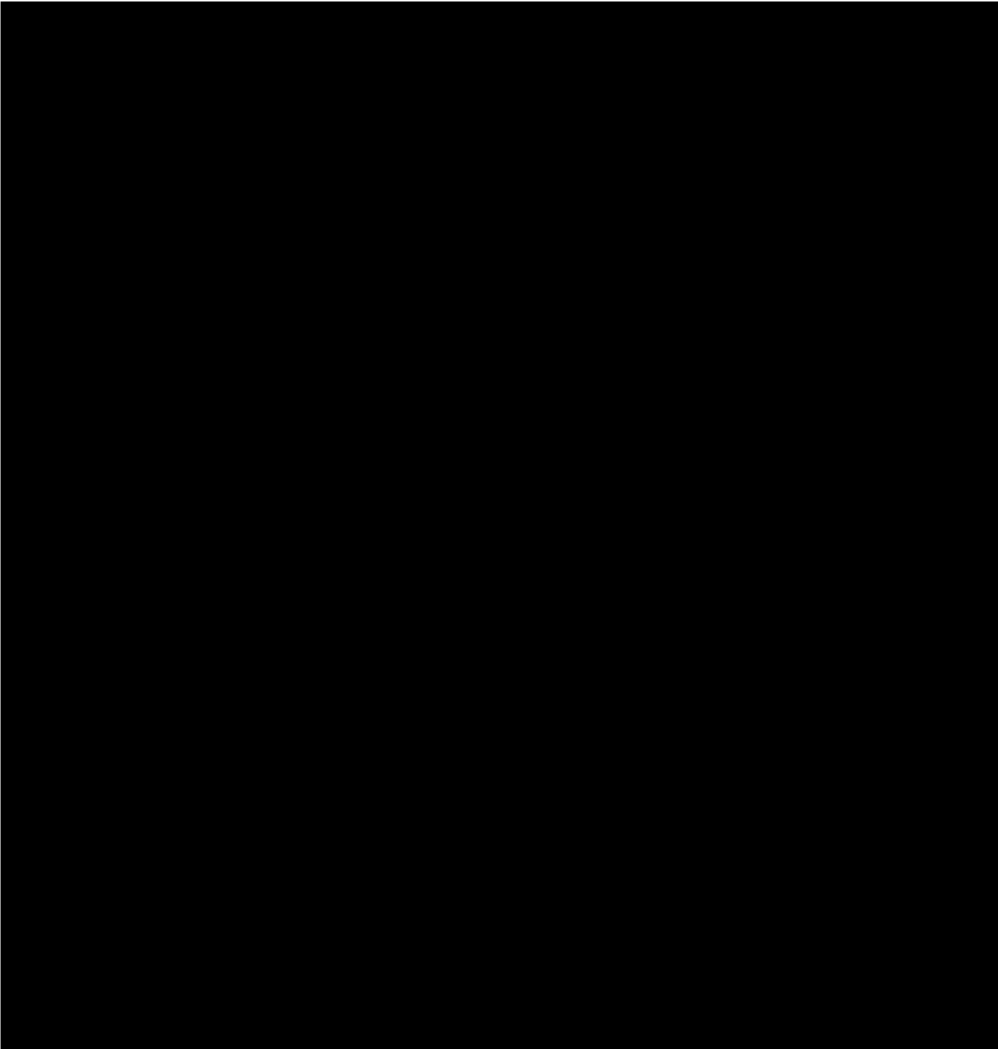
In addition, there are overlapping features with the so-called "subcortical dementias" *(89,90).* This overlap is likely due to the intense connections between the frontal lobes and subcortical regions *(91,92),* as noted in Figure 2.

A history from a reliable informant often reveals major changes in the patient's personality and social conduct, with inappropriate, embarrassing, or impulsive behaviors. Such disruptions often punctuate behaviors that are otherwise characterized by apathy and withdrawal. Changes in appetitive behavior such as eating or sexual activity are common. Patients tend to present in the presenile years (less than 65 years of age). Mental state examination often reveals compromise of the so-called executive functions, including attention, judgment, and insight. Compared to patients with probable AD, patients with

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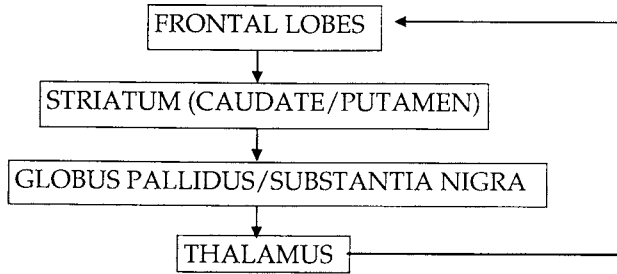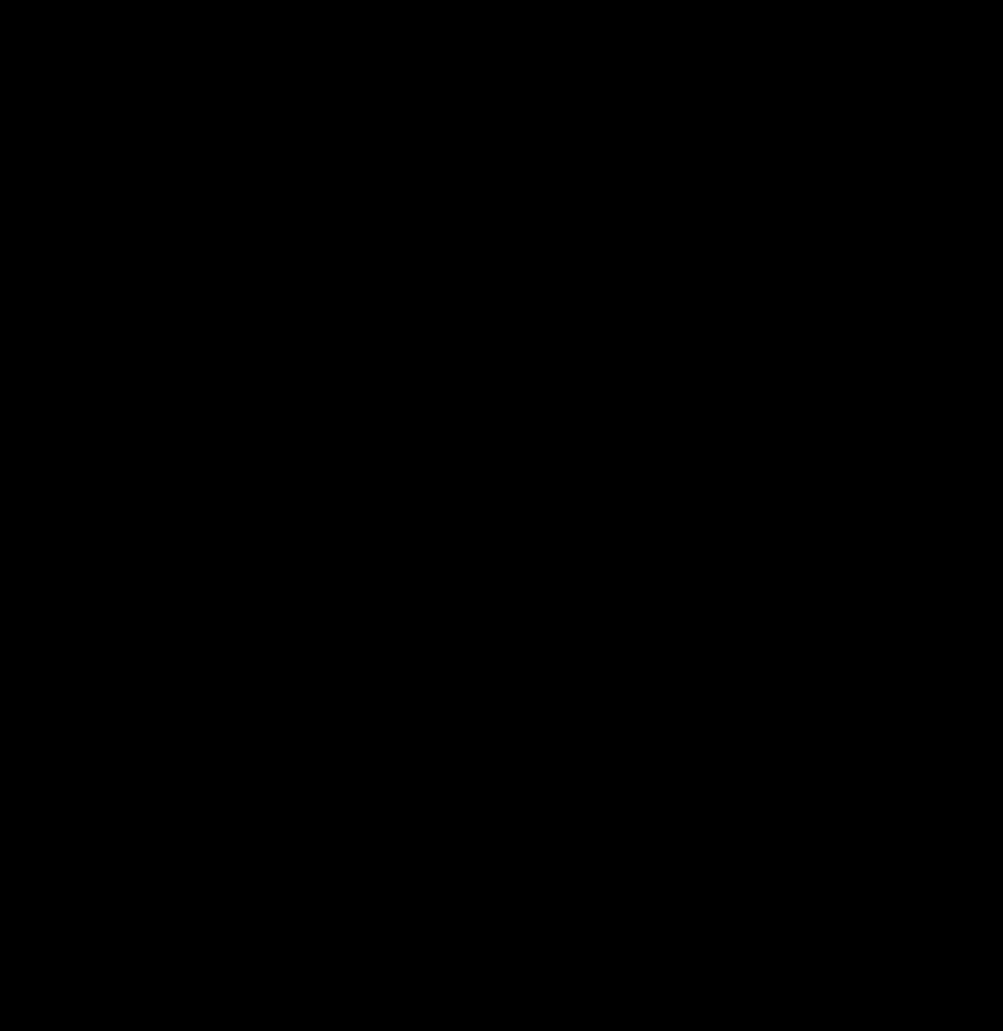
**Fig. 2.**   Schematic view of the frontal networks.

frontotemporal dementia reportedly do better on tests of constructions and calculations *(93)*. Performance in other realms may also be impaired because of a lack of motivation or mental activation. Memory is compromised mainly at the encoding or retrieval stages. With cueing, recognition memory is often relatively well preserved. There is diminished spontaneous verbal output that over time may progress to mutism. CT or MRI tend to show involutional changes in the frontal regions and functional imaging may show diminished perfusion in frontal lobes and anterior temporal regions *(50,51)*. The Lund and Manchester research groups have proposed specific criteria for the diagnosis of frontotemporal dementia, based on behavioral, affective, and cognitive impairments and the results of investigations *(50)*. Table 5 summarizes the diagnosis criteria. The frontotemporal dementias reportedly account for 10–20% of cases of degenerative dementias *(87)*. A recent epidemiological study of the Dutch population suggested that 38% of patients with FTD had a strong family history of dementia (vs. 15% of controls) *(93a)*. Approximately 43% of FTD patients with a family history of dementia were found to have a mutation in the tau gene located on chromosome 17 *(93b)*. Intense interest has developed in investigating the relationship between non-Alzheimer's degenerative dementias and abnormalities linked to chromosome 17 *(93c)*.

On a pathological plane, this dementia syndrome is most often associated with marked atrophy of the frontal lobes and anterior temporal regions and histologically with neuronal loss and gliosis *(30,88)*. Also, 20% of cases also have Pick bodies and ballooned cells, which are pathognomonic for Pick's disease *(88)*. The preponderance of pathology in the frontal lobes and anterior temporal regions accounts for the profile of cognitive and personality changes. This pattern of dementia is rarely associated with the plaque and tangle pathology that defines Alzheimer's disease *(88)*. Lewy body dementia (in which there is widespread distribution of Lewy bodies in brainstem, basal forebrain, and cortex) can present with prominent behavioral changes and has recently been re-

ported as a fairly common form of degenerative dementia with autopsy series suggesting that it may be seen in 15–25% of cases *(94–96)*. Lewy body dementia has been associated with fluctuating cognitive impairment, transient episodes of marked confusion, a high incidence of visual and/or auditory hallucinations and delusions. It is most often accompanied by extrapyramidal signs or heightened sensitivity to a neuroleptic medication.
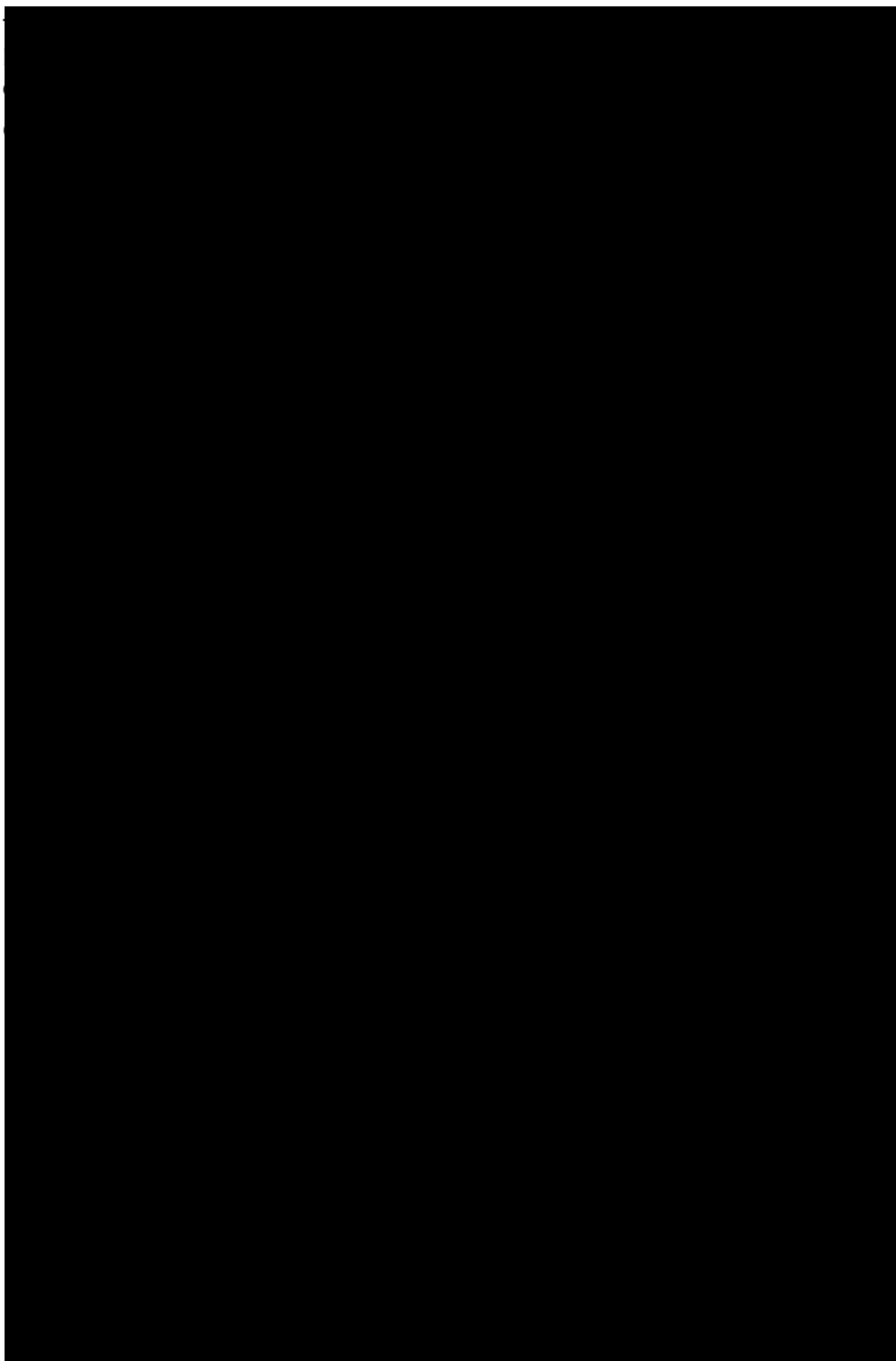
Dementias that exhibit prominent impairments in attention and executive functioning probably have the widest differential diagnosis and constitute many of the potentially reversible conditions. Table 6 provides a list of non-degenerative diseases with prominent changes in attention and behavior that includes the dementia of depression (also known as "pseudodementia"). It has

**Table 6**
**Nondegenerative Disease With Prominent Changes in Attention and Behavior**

Toxic-metabolic disease (e.g., hypothyroidism, or side effects from medications)
Alcohol-related dementia
Space-occupying lesions (especially to the frontal lobe, such as subdural hematoma or
  tumor)
The dementia of depression (also known as "pseudodementia")

been estimated that the dementia of depression accounts for about 5% of de-
mentias in general and about 25% of the potentially reversible causes of de-
mentia *(36)*. On mental state examination, there are often impairments in
attention, concentration, processing speed, and spontaneous behavioral out-
put. Motivation tends to be limited and the patient may complain of not know-
ing the answers, rather than offering incorrect responses. Difficulties with
memory tend to be at the level of encoding and for some retrieval, with rela-
tively preserved recognition memory after delay. There is no aphasia, al-
though word retrieval may be slow. Somatic complaints are not uncommon.
There may or may not be vegetative symptoms or past psychiatric history of
depression. Clinicians should have a low threshold for treating depression,
preferably with medications like the serotonin reuptake inhibitors (SSRIs) that
have relatively low anticholinergic side-effects. Unfortunately, some patients
who initially present with depression go on to exhibit a progressive dementia
despite appropriate treatment for their mood disorder *(97–99)*. In such cases,
the depression was probably an early manifestation of their degenerative
process. It has been shown that patients suffering from degenerative demen-
tias are at increased risk for developing symptoms of depression that often
manifest themselves early in the course of their illness *(100–102)*.

### Dementia Associated with Sensorimotor Signs

A third major pattern in dementia is one in which cognitive decline is accom-
panied by sensory and motor signs. Most often, the salient mental state changes
of these dementias also involve complex attention, behavior, and personality.
Changes in executive functions are not universal, but depend on where the brunt
of the neuropathology is located. Table 7 lists a number of disease processes that
tend to have this dementia profile. The disease entity in this category with the
highest prevalence is vascular dementia. Unfortunately, it is not uncommon for
clinicians to "automatically" render the diagnosis of vascular dementia after a de-
mented patient's MRI or CT scan returns with some evidence of strokes or small
vessel disease. Many autopsy series suggest that the accuracy of clinical diag-
noses of vascular dementia can be quite low (21–82%) *(103,104)*. A large per-

**Table 7**
**Dementias Associated With Sensorimotor Signs**

Vascular dementia
Infection (e.g., HIV, syphilis, Creutzfeldt-Jacob disease)
Metabolic abnormalities (e.g., $B_{12}$ deficiency)
Inherited disorders of metabolism (e.g., metachromatic leukodystrophy, Kuf's disease)
Normal pressure hydrocephalus
Multiple sclerosis
Inflammatory/autoimmune disease (e.g., SLE)
Degenerative diseases with extrapyramidal features (e.g., Parkinson's disease,
  Huntington's disease, progressive supranuclear palsy, and Wilson's disease)
Motor neuron disease with frontotemporal dementia

centage of patients diagnosed with vascular dementia are determined at autopsy to have Alzheimer's pathology, with or without significant cerebrovascular insults *(105,106)*. Although earlier reports of the prevalence of vascular dementia varied widely, recent reviews suggest a prevalence in the United States of around 10% *(15,70,107)*. Symptoms of dementia are reportedly more likely to develop after a critical volume of tissue is infarcted (over 50 mL) or if small strokes are strategically placed that disrupt cognitive abilities *(108)*. Table 8 summarizes the DSM-IV diagnostic criteria for vascular dementia. Diagnosis of vascular dementia is supported by the sudden development of impairments in one or more cognitive domains, a stepwise deteriorating course, focal neurological signs, risk factors for stroke, and a history or imaging evidence of strokes.

If a patient has a history of an insidiously progressive amnestic dementia and is found to have a stroke with sensorimotor signs, a clinician should still consider the diagnosis Alzheimer's disease as likely, but recognize that the cerebrovascular disease may be making an additional contribution to the patient's cognitive impairments. Strokes may reduce "cognitive reserve" in patients and lead to earlier, more dramatic presentations of clinical problems in patients with underlying AD pathology *(109)*. A diagnosis of vascular dementia is probably most tenuous in a demented patient with prominent memory problems, no history suggestive of clinical strokes, and an MRI scan that reveals mild white matter changes and a few T2 signal abnormalities.

As noted on Table 7, there are numerous dementias that are associated with sensorimotor signs of which we will briefly mention HIV associated dementia, neurosyphilis, normal pressure hydrocephalus, multiple sclerosis, and extrapyramidal syndromes. These dementias tend to present with apathy, social withdrawal, blunted affect, diminished behavioral output, and compromised attention. For example, changes in mental state changes can be the presenting

symptoms of HIV infection, although much more commonly there are systemic signs to point to this diagnosis *(110,111)*. Peripheral neuropathy and myelopathy are also commonly seen in HIV infection. The pathology associated with tertiary syphilis tends to be most severe in the frontal and temporal lobes, with associated personality changes, impaired judgment, and altered mood *(112,113)*. Sensorimotor abnormalities commonly accompany the dementia, including dysarthria and changes in gait and reflexes.

Normal pressure hydrocephalus (NPH) is believed to account for about 10% of the reversible dementing illnesses *(36)*. The well-known triad associated with NPH includes gait disturbance, incontinence, and progressive decline in cognitive functioning *(114)*. The pattern of mental state changes seen in NPH usually involves slowed processing speed, impaired complex attention, and diminished executive functioning *(115–117)*. Aphasia and apraxia are unusual and would suggest other contributing etiologies. There is ongoing debate about the best strategies for identifying patients who will benefit most from the placement of a shunt. Normal-sized sulci, periventricular edema, CSF flow void on MRI in the cerebral aqueduct, third and fourth ventricles,

and clinical response to the removal of approximately 30 mL of CSF have been reported to be predictive of better outcomes *(118–120)*. Cisternography does not appear to add much to the information obtained by clinical history and imaging studies *(121)*.

Patients with multiple sclerosis often suffer from cognitive, emotional, and behavioral problems that tend to add to their disability and problems functioning at home and work *(122–124)*. Dementia has been reported in up to a third of patients with Parkinson's disease *(125–128)*. Some patients have co-existing Alzheimer's pathology, which probably accounts for their decline in mental state functioning. Others present with a disruption of frontal networks ("subcortical dementia syndrome") with bradyphrenia, impaired activation, and forgetfulness. These difficulties may reflect diminished dopamine availability to caudate nucleus and prefrontal regions. Medications and coexisting depression also may play an important role. Huntington's disease, progressive supranuclear palsy, and Wilson's disease all have associated mental state changes, which in part reflect the disruption of frontal networks *(89,129–136)*. The associated extrapyramidal features tend to point to the diagnosis in these cases. From 2% to 3% of patients with motor neuron disease present with dementia that has nearly identical features to the frontotemporal dementia that was described earlier *(137,138)*.

### *Progressive Focal Neuropsychological Deficits*

The last major dementia pattern involves progressive neuropsychological deterioration that remains relatively well circumscribed and without prominent memory problems at least in the first 2 years of the illness *(30,139)*. These rare entities serve to remind us that degenerative processes are often relatively selective in their distribution of pathology early in their course. The clinical symptomatology associated with these dementia profiles can be interpreted as reflecting the relatively focal distribution of pathological damage to the nervous system. Primary progressive aphasia has received the most attention *(139–145)*. Other degenerative diseases within this dementia category have been termed slowly progressive apraxia, progressive prosopagnosia, progressive semantic dementia, and posterior cortical atrophy *(146–153)*.

### Summary

This chapter has reviewed the clinical approach to the evaluation of a demented patient. The major branching points along the decision tree of working up the patient were reviewed. We emphasized the importance of clinical judgment in this process, which depends so heavily on a detailed history, mental

status examination, and neurological assessment. We discussed the value of a variety of laboratory tests used by clinicians to assess potentially reversible contributions to a patient's decline in mental state and functional status and noted some of the controversies that have arisen over their cost:benefit ratio.

The chapter reviewed diagnostic criteria, guidelines, and practice parameters offered by major clinical and research bodies. In studies that have employed such guidelines, the accuracy rates for the diagnosis of probable Alzheimer's disease has ranged from 64% to 100%, as determined at autopsy using a variety of standard neuropathological criteria *(1,12,30,154–159)*. Most of the studies achieved a positive predictive value in the mid to high 80s. Such results are very encouraging and are as good as or better than those yielded by many of the experimental diagnostic strategies being investigated. In fact, most of the experimental diagnostic assays have used clinical research criteria as a provisional "gold standard" to diagnose their patients with AD, presumably until a large enough series of their patients has been brought to autopsy.

## Limits of Current Approaches to the Clinical Evaluation of Alzheimer's Disease

If using standard clinical tools can yield such high accuracy rates for diagnosis of AD, why is there a need for other approaches? This important question can be addressed in several ways. First, we are unaware of any systematic study regarding the extent to which most practitioners actually follow the guidelines reviewed in this chapter. There is likely to be a gap between the practice patterns of clinician-researchers in Alzheimer's disease centers and physicians in the community. Practitioners in research centers see a very large volume of demented patients. The impressive accuracy rates reported by such centers may not be due to the fact that the clinicians followed standard guidelines. Rather these particular clinicians may have a wealth of experience upon which they developed the kind of clinical expertise that yields excellent diagnostic results. The extension of such expertise into the community is an important goal, but one that may be very difficult to achieve. We suspect that clinicians in these centers devote more time than average to patients and their families and obtain a detailed history, mental state, and neurological examination. Patients in such centers tend to be followed closely over time. The pattern that emerges with longitudinal evaluations can confirm the initial diagnostic impressions or raise questions about the patient's profile that would lead to even closer scrutiny. Autopsies are often sought, which allows feedback to clinicians on the accuracy of their diagnoses. This kind of intensive, time-consuming review process is unlikely to be carried out in the average community practice.

The accuracy rates in the community have not been as high as in research centers dedicated to the study of Alzheimer's disease and related clinical entities *(160)*. Moreover, autopsy studies on the accuracy of clinical diagnoses in settings that have not utilized careful diagnostic criteria have revealed success rates as low as 55% *(5)*. Given the prevalence of Alzheimer's disease, such a low "hit-rate" suggests a diagnostic accuracy of close to chance. Many of these studies were done during an era in which there was less awareness about the criteria for dementia in general and AD specifically *(16,70)*. Presumably, current accuracy rates would be better, although the economic pressures of modern medicine that encourage clinicians to spend less time with patients than in the past may counter trends toward improvement in diagnosis.

With the exception of the report by Morris and colleagues *(156),* most autopsy series that have demonstrated very high diagnostic accuracy rates have studied patients who were in the moderate to severe stages of the illness. Also, these studies have identified highly selected patients and excluded those with any unusual or complicating features that often arise in clinical practice. Enthusiasm about the accuracy of clinical assessment needs to be tempered by the fact that success rates may be much lower for groups of patients that suffer from a mixture of dementing illnesses, especially those who are in the earliest stages. More importantly, existing diagnostic criteria are not applicable to patients in the preclinical stages of the disease. As treatments become available, identifying AD patients in these stages will become increasinglyimportant.

In summary, studies have demonstrated that clinical assessment, using well established guidelines, can yield very high diagnostic accuracy rates, especially for patients who have reached the moderately severe stages of dementia. The extent to which the average clinician actually follows these guidelines and the degree to which the superb results reported are dependent upon the expertise of a select group of highly trained clinicians have not been determined. The concerns raised in this chapter point to the need to develop additional strategies for identifying AD patients in the preclinical and early stages of the illness. Ideally these strategies would be accessible to clinicians in both research centers and the community.

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