The Handbook of Alzheimer’s Disease and Other Dementias
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The Handbook of Alzheimer’s Disease and Other Dementias

Edited by Andrew E. Budson and Neil W. Kowall
We wish to dedicate this book to our families:

Amy, Leah, and Danny

And

Miriam, Elisheva, Charlotte, Jenny, Mischa, and Jonah
Contents

Contributors ix
Foreword xii
Preface xv

Part I Common Dementias 1
1 Alzheimer’s Disease 3
   Alan M. Mandell and Robert C. Green
2 Vascular Dementia 92
   Angela L. Jefferson, Amanda M. Gentile, and Ravi Kahlon
3 Dementia with Lewy Bodies 131
   Tamara G. Fong and Daniel Z. Press
4 Frontotemporal Dementia 145
   Adam L. Boxer
5 Other Dementias 179
   Peter Morin

Part II Pathogenesis and Disease Mechanisms 195
6 Genetic Risk Factors for Dementia 197
   Paul Hollingworth and Julie Williams
7 The Neuropathology of the Dementing Disorders 235
   Ann C. McKee and Brandon E. Gavett
8 Amyloid Beta Peptide and the Amyloid Cascade Hypothesis 262
   Carmela R. Abraham
9 Other Mechanisms of Neurodegeneration  
Marina Boziki, Vassilis Papaliagkas, and Magda Tsolaki  
277

10 Rational Therapeutics for Alzheimer’s Disease and Other Dementias  
Neil W. Kowall  
301

Part III  Cognitive and Behavioral Dysfunction  
313

11 Memory Dysfunction in Dementia  
Andrew E. Budson  
315

12 Language Processing in Dementia  
Jamie Reilly, Joshua Troche, and Murray Grossman  
336

13 Executive Functioning  
Robert A. Stern, Stacy L. Andersen, and Brandon E. Gavett  
369

14 Emotion and Behavior in Alzheimer’s Disease and Other Dementias  
Christopher I. Wright  
416

15 Visuospatial Function in Alzheimer’s Disease and Related Disorders  
Alice Cronin-Golomb  
457

16 Sleep and Circadian Rhythms in Dementia  
David G. Harper  
483

Part IV  Neuroimaging in Dementia  
505

17 Glimpses of the Living Brain with Alzheimer’s Disease  
Ronald J. Killiany  
507

18 Functional MRI in Alzheimer’s Disease and Other Dementias  
Maija Pihlajamäki and Reisa A. Sperling  
535

19 Molecular Neuroimaging of the Dementias  
Bradford C. Dickerson  
557

20 Using EEG and MEG to Understand Brain Physiology in Alzheimer’s Disease and Related Dementias  
Brandon A. Ally  
575

Index  
604
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Foreword

In 1903, Emil Kraepelin recruited Alois Alzheimer to join his department at the Nervenklinik in Munich. Kraepelin challenged Alzheimer, who was known for his clinical and pathological research, to uncover the biological basis of mental illness. In 1906, Alzheimer hit pay dirt, when he described the neuritic plaques and neurofibrillary tangles in the brain of Auguste D., his 53-year-old patient with dementia. Alzheimer’s presentation at the 37th Assembly of Southwest German Psychiatrists in Tubingen apparently generated very little interest from the attendees, who included such prominent figures as Nissl, Jung, and Binswanger; the Tubinger Chronik newspaper carried a single line on the case in reporting the meeting. Kraepelin’s influential textbook eventually accepted this condition of pre-senile dementia and proposed the name Alzheimer’s disease. Growing from this single case report, Alzheimer’s disease is now widely recognized as one of the most common neurological diseases, but it was not always so.

Between 1906 and 1966, there was very little clinical or research interest in Alzheimer’s disease as it was widely viewed as a rare form of pre-senile dementia. Neurology textbooks rarely allotted it more than a page or two, there were only a handful of papers published in the literature, and almost nothing heard at the annual neurology meetings.

Interest began to pick up with Sir Martin Roth’s report in 1966 that neuritic plaques occurred in brains of the elderly, and that their number roughly correlated with the extent of dementia severity. In 1976, Robert Katzman’s seminal article on the epidemiology of Alzheimer’s disease stressed that pre-senile and senile dementia were similar pathologically. His conclusion that we faced a silent epidemic of staggering proportions was a stunning wake-up call to action. Three other events occurred in the 1970s that catalyzed the modern era wave of clinical and scientific research into the causes, mechanisms, and treatment of Alzheimer’s disease and related dementias. The first of these was establishing the National Institute on Aging at the National Institutes of Health, and the strategic plan for Alzheimer’s
disease under the direction of the Institute’s first director, Robert Butler and the associate director Zaven Khachaturian. This Institute cast Alzheimer’s disease as a priority on the national health stage, and provided federal funds for research. The second important step was led by Jerry Stone, who founded the Alzheimer’s Disease and Related Disorders Association (now renamed the Alzheimer’s Association). This private foundation spread from its base in Chicago to establish chapters across the country dedicated to raising awareness about Alzheimer’s disease and raising money to support research. The third event was a scientific breakthrough: Indices of acetylcholine metabolism, a neurotransmitter in the brain linked to memory capacities, were decreased in brains of patients with Alzheimer’s disease. This advance was crucial because it opened a new approach to Alzheimer’s disease that justified expenditure of public and private dollars for research. Further, this discovery sparked hope for a cure because drugs can be developed that alter the neurochemical milieu of the brain, whereas the anatomic pathological features of Alzheimer’s disease – the neuritic plaques and tangles – have always seemed immutably fixed. Indeed, this discovery paved the way for developing acetylcholinesterase inhibitors, the first class of drugs approved by the FDA for treating Alzheimer’s disease. In 1984, the first clinical criteria for the diagnosis of Alzheimer’s disease was published, and the first five Alzheimer’s Disease Research Centers were established with funding from the National Institute on Aging. These Centers, which now number 30 across the United States, are the focal point for much of the clinical and scientific research conducted on Alzheimer’s disease. This volume highlights many of the advances generated by investigators in these Centers and underscores the multidisciplinary approach in clinical science that is the hallmark of modern dementia research.

Alzheimer’s disease is the most prevalent cause of dementia, but not the only cause. Dementia due to multiple strokes has always been appreciated, but clinicians now routinely diagnose degenerative conditions such as frontal temporal dementia and diffuse Lewy body disease that were previously lumped with Alzheimer’s disease. As pointed out in chapters of this volume, these related neurodegenerative diseases have clinical and neuropsychological features that aid in the diagnosis and that distinguish them from Alzheimer’s disease. In this sense, the field of cognitive neuroscience has improved the diagnosis of dementia syndromes; in turn, the study of neurodegenerative diseases has helped boost neuropsychological research. Neuroimaging also helps distinguish Alzheimer’s disease, frontal temporal dementia, and dementia with Lewy bodies, as brain scans in each of these conditions have a typical anatomic, functional and molecular signature. Their separate identities are reinforced by neuropathological findings that confirm the clinical diagnoses, and that also drive scientific research into the causes of each disease. Advances in this area now permit molecular classification of diseases due to accumulation of misfolded proteins in brain that are distinctive for each condition. Thus, we speak of Alzheimer’s disease as an “amyloidopathy”; some cases of frontal temporal dementia as a “tauopathy”; and dementia with Lewy bodies as an “alpha-synucleinopathy.” Uncovering the molecular signature of these diseases is as
important to the field now as the discovery of acetylcholine deficiency was in the
1970s, as research into the cellular mechanisms leading to accumulation of toxic
protein fragments may hold the key to developing protective and even curative
therapies.

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Preface

This book provides a comprehensive review of Alzheimer's disease and other dementias from both basic and clinical neuroscience perspectives. Scientists and medical professionals will find both a broad introduction and an up-to-date review of important scientific advances in a single volume. Those working in the areas of Alzheimer’s disease and dementia will find this book of interest, including physicians, medical students, psychologists, scientists, graduate students, and allied health professionals including nurses, social workers, and therapists. Part I, “Common Dementias,” is designed to provide an overview of Alzheimer’s disease and other dementias including a brief discussion of pathology, pathophysiology, clinical manifestations, diagnosis, and treatment. It also provides background for later chapters. Part II, “Pathogenesis and Disease Mechanisms,” provides an update on the current genetic risk factors and pathophysiological mechanisms related to dementia. Part III, “Cognitive and Behavioral Dysfunction,” reviews the disruption of different cognitive and other functions, including emotion and sleep. Part IV, “Neuroimaging in Dementia,” provides an update on this exciting and fast-paced field. The book is designed such that readers can either peruse a chapter of interest or read the book cover to cover. In either case, we believe that you will find this book a useful tool for school, research, or clinical practice.

We would like to thank all of our authors for their excellent contributions and the series editor Professor Mostofsky for his constant encouragement. It is they who deserve the credit for the value in this book; any errors contained herein are our fault alone. Lastly, we would like to note that this book was completed entirely on our own time, during late nights, early mornings, weekends, and vacations.

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Part I
Common Dementias
Alzheimer’s Disease

Alan M. Mandell and Robert C. Green

History

In 1871, over 30 years before Alois Alzheimer published his seminal cases, James Crichton-Browne may have been among the first physicians to remark upon the relationship between “brain wasting” and “premature dotage” in a letter to Charles Darwin (Snyder & Pearn, 2007). Age-related mental deterioration as an entity had been recognized virtually for recorded history (Boller et al., 2007; Mandell & Albert, 1990). Emil Kraepelin, however, was one of the few 19th-century giants of medicine who recognized the connection between brain pathology and mental dissolution in the elderly (Stam, 1985). He referred to “Morbus Alzheimer” as early as 1908 and used the eponym in the 1910 edition of his textbook (Kraepelin, 1910). Over the next century plus, Alzheimer’s disease (AD) has become the focus of one of the most intensive investigations in medical history. A Google search for AD now generates over 18 million hits.

Alzheimer examined 51-year-old Auguste D. in 1901 (Graeber, 2006). Her husband had noted a relatively sudden change in her behavior, dominated by panic, terror and suspicions of his having an affair with a neighbor. She neglected her housework, hid objects and fumbled in the kitchen. Over the next several months, she became increasingly restless and a disturbance to their neighbors. By the time of her admission to hospital, which she never left, she suffered from “weakening of memory, persecution mania, sleeplessness, restlessness,” had an “amnestic writing disorder,” was unable to perform any mental or physical work and was “rarely free from fear and agitation.” Periods of calm cooperation alternated with physical aggression towards other patients, “groping their faces as if she were blind” (Page & Fletcher, 2006).

Alzheimer was met with silence when he first presented his case (Alzheimer, 1906) of “a distinct disease process” (Nair & Green, 2006). Following his initial publication...
of 1907 (Alzheimer, 1907), he issued his classic review article in 1911 (Alzheimer, 1911).

With a few exceptions and for several reasons (Nair & Green, 2006), “Alzheimer’s disease” for roughly the next 50 years denoted “presenile” dementia and differed from the “normal” senility associated with old age, despite Alzheimer’s assertion that there were no significant pathological differences between older and younger cases (Spielmeyer, 1916). Kraepelin as well opined that this illness is “a peculiar disease process that is largely independent of age” (Kraepelin, 1910).

Alzheimer described the now familiar distinctive pathology in his original 1907 article. Slides from two patients were rediscovered in 1992 and 1997, and those from Auguste D. clearly demonstrate numerous characteristic cortical plaques and tangles (Graeber, 2006).

**Epidemiology of Dementia and AD**

In virtually all developed countries, the oldest segments of society are increasing at the fastest rate and an epidemic of age-related diseases is already upon us. The dementia syndrome is largely a provenance of the elderly and is a major part of a looming public health crisis. The global prevalence of dementia of any cause in 2005 was about 24 million with yearly incidence of almost 5 million, tantamount to adding a new case every 7 seconds (Ferri et al., 2005).

AD accounts for about 55–70% of adult-onset dementia in the industrialized world (Lim et al., 1999), is the fifth leading cause of death in Americans older than 65, and, in contrast to the decreasing death toll attributable to other major diseases, that due to AD is on the rise (Mebane-Sims & Alzheimer’s Association, 2009) (Figure 1.1).

![Figure 1.1](image)
AD incidence is age related and doubles about every 5 years from age 65 through the 90s (Bachman et al., 1993; Berlau, 2007). The exact prevalence of AD is difficult to determine because, among other reasons, death certificates of people with end-stage AD often list infection or “cardiopulmonary arrest” as the proximate cause. Currently, over 5 million Americans have AD with incidence of a new case about every 70 seconds. In the United States, there will be at least 8.5 million people with AD by the year 2030, about 13 to 25 million in 2050 (a new case every 33 seconds) (Hebert et al., 2003; Mebane-Sims & Alzheimer’s Association, 2009) plus an unknown number with other dementias. National direct and indirect monetary costs of caring for people with Alzheimer’s disease alone is already at least $100 billion annually in the United States (Koppel, 2003), where nursing home cost per patient currently hovers around $50,000 per year, and over $300 billion per annum globally (Dartigues, 2009). We therefore need hardly emphasize the current and growing economic impact of AD, the “coming plague of the 21st century,” on health systems worldwide. More specific epidemiological data are discussed in this and other chapters.

Dementia

Definition, evaluation, management, and treatment

Symptoms common to most dementias include forgetfulness, language deterioration, mood changes, impaired judgment, and loss of initiative. There is nevertheless no universally accepted definition of “dementia,” which has been broadly characterized as a syndrome, as shorthand for unsuccessful aging, and as a specific diagnosis (Green, 2005), that is, as a synonym for AD. Within its multitude of definitions, diagnostic criteria have routinely included memory impairment, decline in social or occupational function (American Psychiatric Association, 2000), progressive deterioration, incurability, and irreversibility. Clinicians must nevertheless be aware that pathological processes underlying many causes of dementia are static and that a few are treatable. Furthermore, while the association between dementia and memory disorder is almost ubiquitous, significant amnesia is not a salient feature of every dementing disease. Evidence of functional decline, e.g., in personal hygiene, bill paying, housecleaning, personality, etc., is, at least for research purposes, currently the clinical marker separating “possible dementia” and “normal aging” from “dementia.” Many factors can nevertheless mask or delay occupational or social incompetence and we favor a somewhat broader definition.

“Dementia,” as used in this chapter, is a syndrome of acquired persistent intellectual impairments characterized by deterioration in at least three of the following domains: memory, language, visuospatial skills, personality or behavior, and manipulation of acquired knowledge (including executive function) (Cummings, 2004; Cummings & Benson, 1992; Cummings & Mega, 2003). According to this definition, mental retardation and acute confusional states (ACS; delirium) do not qualify, the
former because it is not acquired, the latter because multiple cognitive impairments associated with it by definition are temporary (see subsequent discussion of the ACS). The presence of a dementia is supported by a combination of a carefully obtained history, physical and mental status examinations, significant impairment on neuropsychological tests corrected for age and education, and a change in test scores over a 6–12-month interval (Mesulam, 2000).

This definition, like all the others, is not perfect. Persons with superior premorbid intellect and greater cognitive reserve (Roe et al., 2007) may suffer decline in occupational performance which nevertheless escapes even the most detailed clinical assessment and which results in no other objective functional impairment (Cummings, 2005a; Strub & Black, 2000). Some ultimately dementing disorders (Benson et al., 1988; Dubois et al., 2007; Mesulam, 2003) may manifest for years as gradual deterioration limited to a single cognitive domain which in turn can influence execution and interpretation of other cognitive functions (Mesulam, 2000).

“Dementia of the Alzheimer type” (DAT) refers to the clinical syndrome which by far is that most commonly associated with autopsy-proven (pathologic) AD.

**Recognition and differential diagnosis of the dementia syndrome**

Management and treatment of dementia begins with its recognition, which is reasonably straightforward either when the patient or an independent historian expressly raises cognitive (or behavioral) deterioration as an issue, or it becomes obvious in context with other medical issues (e.g., following hospital admission). Recognition is a not inconsiderable concern, however, because cognition and behavior are indeed not issues for many “community dwelling elderly” who are nevertheless already demented and just one fall, infection, change of address or assault of a spouse away from health system entry for these issues (Albert et al., 1991).

Recognition is further hindered because widespread neuropsychological testing, imaging and laboratory screening for asymptomatic elderly people is not economically feasible. Furthermore, many health professionals as well as lay people persist in believing that cognitive loss is an inevitable and “natural” consequence of aging rather than a reflection of brain damage. Although there is some longitudinal evidence that general cognition “normally” recedes in a person’s mid-70s (Brayne et al., 1999), much of the decline previously attributed to age alone probably reflects the effect of mild unrecognized dementia. Studies of optimally healthy older adults who are evaluated each year suggest that overall cognitive function may slow somewhat but does not reflect a significant longitudinal decline for these persons (Schaie, 1989). Therefore, in the absence of disease, older adults can reasonably expect stable overall cognitive function and little or no interference with performance of everyday activity (Rowe & Kahn, 1987). This requires a fundamental shift in the approach to the aging patient, in that clinicians should not automatically attribute memory or cognitive problems that interfere with everyday activities to normal aging, and this should be communicated to the patient’s family.
Among adults over 85 years of age, the definition of “normal” cognition is much more difficult to establish. Many neuropsychological tests have not been validated for this group of the “oldest old,” and vision and hearing problems often interfere with assessment. Apparently unimpaired individuals over 85 are nonetheless at high risk of cognitive decline (Crystal et al., 2000; Howieson et al., 2003).

Most clinicians do not routinely test mental status in older individuals unless they receive complaints either from the patient or the patient’s family. Many demented patients do not, however, so-complain and, on average, most family members do not seek medical attention for the patient until several years after onset of symptoms (if the dementia is progressive). Most patients with DAT, therefore, escape early diagnosis, particularly in primary care settings (Callahan et al., 1995; Cummings, 2004; Cummings & Mega, 2003; Dartigues, 2009; Petrovitch et al., 2001). Cognitive symptoms that are not associated with obvious functional impairment may be dismissed or minimized.

The prevalence of truly curable dementia in the community has been debated (Clarfield, 1995; Weytingh et al., 1995). The probability of finding a reversible cause for dementia has nevertheless likely declined greatly in the past 20 years (Clarfield, 2003; Mok et al., 2004). Prompt recognition of dementia remains important all the same because emerging diagnostic techniques and increasingly effective therapeutic interventions are altering the definition of “treatable” (Fagan et al., 2007). Advantages of an early-as-possible diagnosis of dementia are listed in Table 1.1.

### Differential diagnosis of the dementia syndrome

Dementia is a syndrome of multiple possible causes. Like anemia, dementia is a differential diagnostic, not a diagnostic term. In other words, even though AD would for most demented persons be a correct diagnosis, the clinician should systematically consider other disorders. Drugs (polypharmacy!), depression, and

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**Table 1.1** Advantages of early diagnosis in dementing conditions

<table>
<thead>
<tr>
<th>For every case</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provide a diagnostic answer and education for the patient and/or family</td>
</tr>
</tbody>
</table>

**For patients with reversible or static diseases (e.g., depression, stroke)**

<table>
<thead>
<tr>
<th>For patients with irreversible and progressive diseases (e.g., Alzheimer’s disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treat cognitive and behavioral symptoms</td>
</tr>
<tr>
<td>• Plan legal and financial future while patient is still competent</td>
</tr>
<tr>
<td>• Initiate management strategies that will postpone dependence and institutionalization</td>
</tr>
</tbody>
</table>

metabolic disturbances are relatively common causes of the dementia syndrome (alone or in combination with AD) and are at least partially treatable if not frequently fully reversible (Clarfield, 1988). Important categories and diseases to consider are summarized in Table 1.2, many of which are further discussed in this and other volumes (Cummings & Benson, 1992; Cummings & Mega, 2003; Lerner & Whitehouse, 1994; Mesulam, 2000).

Depression, a very common ailment of the elderly, is worthy of special mention. Disturbances of thinking and memory frequently accompany depression and have led to the use of the misleading term “pseudodementia.” Since depression can cause authentic, often but not always reversible functional cognitive impairment, a more appropriate designation would be the dementia syndrome of depression (DSD).

Application of the differential diagnosis assumes the examiner’s clinical skills, competence and perseverance in gathering information, and recognizing patterns of neuropsychological impairments. A detailed mental status examination tutorial is beyond the present scope but following is a summary, and further guidance can be found elsewhere (Mandell, 2010; Strub & Black, 2000).

**Dementia evaluation**

The evaluation process includes physical and mental status examinations, ancillary studies and, most importantly, history. We cannot overemphasize the requirement for an independent, reliable historian, that is, someone other than the patient. Easily emphasized, this requirement is often not practical because elderly patients often live alone or are otherwise socially isolated. Furthermore, there is no guarantee that family members’ or friends’ histories are more reliable than that of the patient. For example, family members sometimes attribute actual cause to triggers such as fever, minor surgery, new stresses or a disorienting vacation because subtler symptoms have previously been missed or ignored. Some informants, including spouses, may be embarrassed or otherwise less than forthcoming about alcoholism, physical aggression or sexual indiscretions in the patient’s presence; for this reason it’s often helpful to interview the informant, particularly a spouse, separately. Other informants, including family members and business associates, may lie.

History taking often illuminates obvious functional impairments. Sometimes, however, there has been no significant activities of daily living (ADL) or occupational deterioration. The examiner should therefore attempt to determine whether the patient has had any consistent decline from his or her usual level of competence. For example, a university professor may complain that he or she can no longer teach a familiar class without notes, while someone working with fewer high-level cognitive demands may not notice problems in the workplace but may neglect paying the bills. A problem with evaluating the former is that of “ceiling effect”: limited sensitivity to change by any test in very mildly impaired subjects. That is, even extensive neuropsychological testing may fail to detect significant deficits. Such people would not be classified as “demented” by most current criteria. Highly educated persons with minimal or no cognitive symptoms or signs may nevertheless harbor high plaque and tangle counts, enough to satisfy current pathological criteria.
Table 1.2  Differential diagnosis of the dementia syndrome

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Important examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Prion diseases, syphilis, Lyme disease, chronic meningidites, HIV, Whipple’s disease, hydrocephalus</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>Primary or metastatic tumors, (particularly of the frontal lobe), paraneoplastic encephalitis, disseminated intravascular lymphoma, hydrocephalus</td>
</tr>
<tr>
<td>Traumatic brain disease</td>
<td>Chronic subdural hematoma, contusions, diffuse axonal injury, hydrocephalus, dementia pugilistica</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Multiple sclerosis, primary CNS angiitis, lupus and other vasculitides, sarcoid</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Renal and hepatic failure, hyper/hypo-thyroidism/calcaemia/natremia, Wilson’s disease, metachromatic/adrenoleukodystrophy GM₂ and other gangliosidoses Pantothenate kinase deficiency</td>
</tr>
<tr>
<td>Toxic disorders</td>
<td>POLYPHARMACY Drugs: antidepressants, anxiolytics, sedatives, hypnotics, anticholinergics, neuroleptics, multiple cardiac and antihypertensive drugs, narcotics, lithium, antineoplastics, antiepileptics Metals (arsenic, thallium, lead, manganese) Industrial agents (CCl₄, CS₂, TCE, organophosphides) Radiation encephalopathy Alcohol and other drugs of abuse</td>
</tr>
<tr>
<td>Nutritional/Deprivation</td>
<td>B12/Folate and other vitamin deficiencies Wernicke–Korsakoff syndrome</td>
</tr>
<tr>
<td>“Degenerative” dementias</td>
<td>Alzheimer’s disease Frontotemporal and Parkinsonian dementias Huntington’s disease Neuronal ceroid lipofuscinosis</td>
</tr>
<tr>
<td>Vascular dementias</td>
<td>Multiple infarct dementia “Binswanger’s disease” “Small vessel ischemic disease” CADASIL</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Schizophrenia Dementia syndrome of depression Bipolar disorder Malingering Obsessive compulsive disorder</td>
</tr>
</tbody>
</table>

CCl₄ = carbon tetrachloride; CS₂ = carbon disulfide; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS = central nervous system; HIV = human immunodeficiency virus; PML = progressive multi-focal leukoencephalopathy; TCE = trichlorethylene; pantothenate kinase deficiency = Hallervorden–Spatz disease
for AD. Their substantial “cognitive reserve” allows them to remain relatively asymptomatic despite extensive pathology although once (if) symptoms develop, they endure shorter duration of disease before death (Portet et al., 2009; Roe et al., 2008; Roe et al., 2007). Persons with limited education, in less demanding jobs, or those who were already significantly impaired prior to the onset of the dementing illness, in contrast, are vulnerable to “floor effect,” a similar test insensitivity to change leading to overestimation of cognitive impairment.

If adequate information acquisition is possible, the following should be included:

- **Present history** – sudden versus insidious onset; precipitating event; relatively steady decline or remarkable fluctuations or prolonged periods of return to “normal” function; social skills, work, driving, hobbies, community activities, hygiene and eating behavior, housekeeping; sleep (nocturnal behavior; daytime somnolence).
- **Past/Social history** – alcohol or other substance abuse including tobacco; all current medications (including vitamin supplements); head trauma; psychiatric illness (particularly depression); surgical procedures; stroke and other vascular disease; cancer; sleep disorders.
- **Family history** – dementia; “senility”; “trouble with memory loss like his/hers when older”; “hardening of the arteries” and depression in any first-degree relative, if known.

Office testing of cognitive function should be performed on every person over the age of 65 in an attempt to distinguish demented from nondemented persons and thus inaugurate evaluation of the former. What constitutes “office testing” is often determined by the realities of practice type, time constraints and reimbursement. Many brief cognitive rating scales have been published in response to these realities, through which it is possible to get a reasonable notion of cognitive capacity (“mental status”) (Mandell, 2010). These tests are simple to administer, require relatively little training, are in general valid for the functions being assessed, and usually boast good inter-rater and test–retest reliability.

**Screening tests**

All screening tests have their pros and cons since all are surrogates for more extensive neuropsychological testing. Some are highly verbal thus penalizing patients with relatively more profound language impairment or limited education. Some are directed to the patient, others are informant-based (generally more sensitive) (Tierney et al., 1996), some are dual purpose and all can be combined with elements from other tests to increase sensitivity and specificity (Galvin, Roe, & Morris, 2007), albeit at the expense of additional administration time. In general, all are relatively insensitive to mild cognitive and behavioral impairments and many are subject to educational, racial, cultural, and age biases. Some investigators have even recommended against screening in the absence of truly effective treatments for AD (Boustani et al., 2003).
The most commonly used brief rating scale is the Mini-Mental State Examination (MMSE) (Albert, 2008; Folstein et al., 1975; Mandell et al., 1994). Its advantages are its brevity, ease of administration, and accuracy in detecting moderate dementia. Used sequentially over several years, moreover, scores, in general, track cognitive decline, if any, reasonably accurately. Nevertheless, the MMSE suffers from insensitivity and both floor and ceiling effects, is very language dependent, culturally insensitive, and has limited value as a method to mark cognitive changes in people with AD in short clinical trials (Bowie et al., 1999; Clark et al., 1999).

A published brief informant-based test, the AD8 (Galvin et al., 2005), appears to distinguish dementia from nondementia reasonably well and may also be useful as a self-assessment tool in the absence of an informant, at least when dementia is mild (Galvin et al., 2007).

Other popular instruments include the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), the Montreal Cognitive Assessment (www.mocatest.org) and 7-Minute Screen (Solomon et al., 1998).

**Mental status testing**

If you are the clinician to whom a patient has been referred specifically for neurobehavioral issues, however, these scales often are inadequate and office or bedside mental status evaluation, tempered in consideration of the patient’s educational and cultural background, should include at least brief assessments of attention, language, praxis, visuospatial, memory, and executive functions. Assessment of attention is particularly important because the remainder of the mental status examination will be nonspecifically impaired by inattention. Also recognize that all of these domains are functionally interdependent. Copying a clock face, for example, requires sequencing (“executive”) skill and attention as well as visuoperception. Selected tests include:

- **Attention**: digit span forwards, reciting months of the year in reverse, serial subtractions.
- **Language**: object and body part naming, assessment of spontaneous conversation (fluent or non-fluent speech), at least auditory comprehension, preferably reading comprehension as well; word-list generation and repetition (Green, 2005; Jorm et al., 2007; Knopman & Ryberg, 1989).
- **Praxis**: three or four transitive limb actions (hair combing, screw driving, teeth brushing, hammering, coin flipping), which are somewhat more sensitive than intransitive actions (waving goodbye, saluting) (Rapcsak, Croswell, & Rubens, 1989).
- **Visuospatial**: copy an analog clock face or a complex line drawing.
- **Executive**: clock drawing to command, proverb interpretation, similarities (e.g., between an apple and a grape, or a poem and a statue), coin switch test, cursive alternate writing of the letters “m” and “n” (Mandell, 2010).
- **Memory**: while assessment of orientation, delayed recall of several unrelated words, current events and verifiable biographical information are fine for overtly demented patients, we recommend adding the relatively brief drilled word span
and Three Words–Three Shapes (TWTS) (Weintraub, 2000) tests to mental status testing to capture more subtle memory deficits in dubious cases. Either adds several minutes to the encounter, but the information derived usually justifies the effort. The TWTS test is particularly useful because it assesses incidental learning (affected early in AD), both verbal and nonverbal episodic memory, and enhances encoding by minimizing the effect of inattention.


Ancillary testing for dementia
Time constraint, type or lack of insurance, availability of ancillary testing, and patient or family cooperation are important issues. A combination of neuropsychological, serologic, and spinal fluid testing is often employed, but these services are out of reach for many patients. Even when available, which tests should be performed depends on the source of the recommendation. Full batteries of laboratory tests and at least one brain magnetic resonance (MR) scan are recommended by many (Blennow et al., 2006; Cummings & Benson, 1992; Green, 2005; Knopman et al., 2001); others argue that this is a costly shotgun approach unlikely to determine a treatable cause in the vast majority (Clarfield, 1988; Siu, 1991).

Including B12, folate, and TSH levels, for example, is a point of some contention. Treatment of B12 encephalopathy, if instituted early, improves some functions, but not others, including memory (Freidenberg & Drake, 1990). Furthermore, high-dose B vitamin supplementation fails to slow cognitive decline in patients with presumed AD (Aisen et al., 2008). The American Academy of Neurology (AAN) Practice Parameter (Knopman et al., 2001), acknowledging that the association of B12 deficiency and hypothyroidism with dementia is not clear and that treatment of same in cognitively impaired people often yields no improvement, nevertheless recommends B12 (and TSH) measurement at guideline level.

If ancillary testing is available (and allowed), most clinicians still check, and we recommend: CBC, B12, TSH, liver and renal function. We also recommend brain MRI or, if not possible, at least a noncontrast brain CT scan (Knopman et al., 2001). MRIs in the elderly often demonstrate nonspecific “atrophy” and equally nonspecific scattered bright T2 white matter signals (leukoaraiosis; “microvascular white matter ischemic changes”). The aim of clinical neuroimaging is two-fold:

- to rule out (or in) significant abnormalities that are themselves treatable (e.g., chronic subdural hematoma, meningioma) or indicative of correctible underlying disorders (hypertension);
- to identify such specific perturbations as neoplasms, small or large infarcts, focal atrophy, infections which one could reasonably implicate as a cause of cognitive decline.