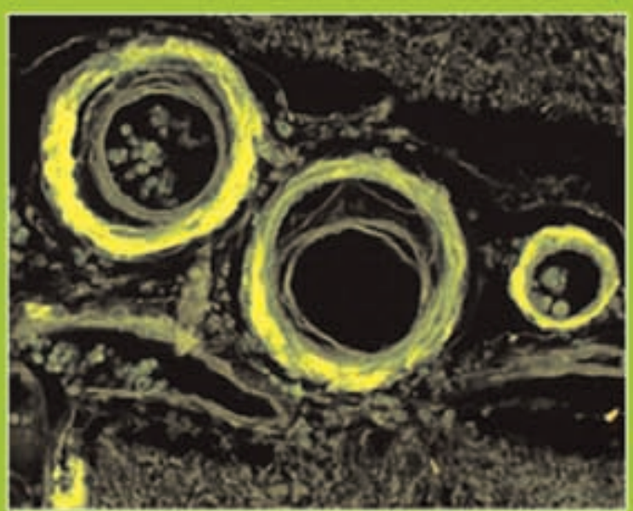
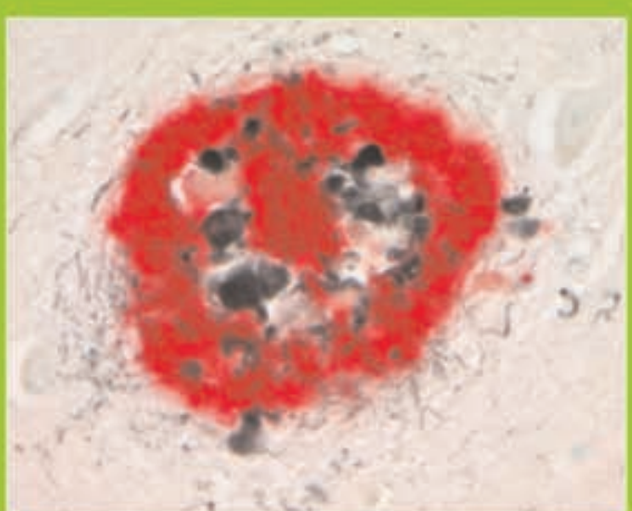
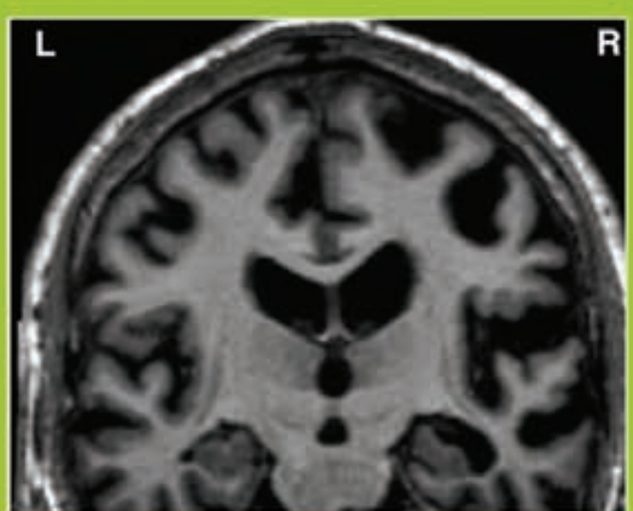
An Atlas of Investigation and Diagnosis

DEMENTIA

Daniel W McKeel, Jr • Jeffrey M Burns • Thomas M Meuser • John C Morris







CLINICAL PUBLISHING

An Atlas of Investigation and Diagnosis

DEMENTIA

Daniel W McKeel, Jr
Alzheimer's Disease Research Center
Washington University School of Medicine
St Louis, Missouri, USA

Jeffrey M Burns
Alzheimer and Memory Program
University of Kansas School of Medicine
Kansas City, Kansas, USA

Thomas M Meuser
Alzheimer's Disease Research Center
Washington University School of Medicine
St Louis, Missouri, USA

John C Morris
Alzheimer's Disease Research Center
Washington University School of Medicine
St Louis, Missouri, USA

CLINICAL PUBLISHING
OXFORD

Clinical Publishing
an imprint of Atlas Medical Publishing Ltd
Oxford Centre for Innovation
Mill Street, Oxford OX2 0JX, UK

Tel: +44 1865 811116
Fax: +44 1865 251550
Email: info@clinicalpublishing.co.uk
Web: www.clinicalpublishing.co.uk

Distributed in USA and Canada by:
Clinical Publishing
30 Amberwood Parkway
Ashland OH 44805 USA

tel: 800-247-6553 (toll free within U.S. and Canada)
fax: 419-281-6883
email: order@bookmasters.com

Distributed in UK and Rest of World by:
Marston Book Services Ltd
PO Box 269
Abingdon
Oxon OX14 4YN UK

tel: +44 1235 465500
fax: +44 1235 465555
e mail: trade.orders@marston.co.uk

First published 2007

A catalogue record of this book is available from the British Library

ISBN 978 1 904392 37 8

Electronic ISBN 978 1 84692 545 0

Printed by T G Hostench SA, Barcelona, Spain

Contents

Preface

Knowledge about the clinical, neuropsychological, neuroimaging, biochemical, molecular, and neuropathological characterization of neurodegenerative dementing disorders is rapidly growing. This atlas was conceived as a compendium of clinical and neuropathological descriptions of these features and is intended to inform all who are interested in the dementing disorders, including students, postdoctoral trainees, health care professionals, practicing physicians, and scientists. The emphasis is on clinical and pathological differential diagnosis.

This atlas is not meant to be a comprehensive treatise but rather a focused review that can be used to gain a rapid and up-to-date perspective on key features of dementing neurodegenerative disorders. The neuroimaging and pathologic illustrations and the literature citations in each chapter are selected to enhance the reader's understanding of disease expression and differential diagnostic features. We include both seminal and recent references with preference being given to reviews. We believe in establishing reliable clinicopathological relationships that assist in arriving at an accurate final diagnosis as a critical element in the effort to assess new treatments and in presenting new research findings.

Each chapter includes summary tables of core clinical and neuropathologic features of the disease or disease family being discussed. An exhaustive coverage of each topic is beyond the scope of this monograph; several excellent books cover specific topics in more depth.

The atlas was authored by clinician-scientists from the Alzheimer's Disease Research Center (ADRC) at Washington University in St Louis, Missouri, and at the University of Kansas School of Medicine, in Kansas City, Kansas, USA. As such, it reflects the contributions of our many colleagues and collaborators who have influenced us in numerous important ways. Chief among these influences is the ADRC's focus in the clinical distinction of early-stage dementia from nondemented aging by eliciting evidence of intraindividual cognitive decline from previously attained levels and on the validation of these distinctions through clinicopathological correlations.

Chapter 1 is a clinical overview of dementing disorders. The diagnosis of these disorders focuses on Alzheimer's disease (AD) because it is by far the most common cause of dementia in older adults. The growing role of neuroimaging in clinical settings and in research is also discussed.

Chapter 2 presents an approach to the behavioral assessment of AD dementia with neuropsychological tests.

Chapter 3 addresses autopsy and histopathological methods used in the ADRC's Neuropathology Core to diagnose various adult dementias in over 1,050 brains from longitudinally characterized research subjects. Routine histopathologic, special dye and silver stains, and immunohistochemical techniques as well as specialized autopsy techniques for brain, cerebrospinal fluid, and pituitary gland removal are presented and illustrated. Selected staining protocols used in the ADRC Neuropathology Core laboratory are presented in the Appendix.

Chapter 4 covers the spectrum of aging-associated neuropathologic findings that form the necessary baseline for assessing abnormalities caused by dementing disorders. Even today, our knowledge base of these important features of healthy or 'normal' brain aging are incompletely defined.

Chapter 5 focuses on the neuropathology of AD. Our research indicates that AD pathology may begin in the sixth decade of life or even earlier with focal deposition of preamyloid and diffuse beta amyloid plaques, accompanied by very focal formation of pretangles and tangles in certain specific cerebral regions. The lesion profiles are associated

with very mild, mild, moderate, and severe dementia as defined by the Clinical Dementia Rating (CDR), which was developed in 1982 by Leonard Berg, Charles Hughes, and colleagues at the predecessor to our ADRC and was updated by John C Morris in 1993. The chapter also discusses the roles of vascular disease and cerebral amyloid angiopathy and cerebrovascular lesions as they interact with other features of AD pathology.

The following chapters deal in turn with vascular dementia (Chapter 6), Lewy body dementias as synucleinopathies (Chapter 7), and frontotemporal dementia (FTD) syndromes as types of tauopathies (Chapter 8). Chapter 9 briefly surveys a number of less common dementing illnesses to provide readers with an idea of the full range of clinical conditions and pathologic lesions that are associated with dementia. It is our hope that readers will develop a sense of the interplay of clinical expressions of the various disorders with the underlying brain lesions that reflect disturbances of basic cellular and molecular processes.

We acknowledge with gratitude the large team of physicians in several specialties, nurses, psychologists, basic scientists, and others who make the ADRC a wonderfully stimulating environment in which to work and ultimately have made this book possible. We also are indebted to our research participants and their families who unstintingly give their time and support to the ADRC's efforts to conquer the dementing illnesses. The ADRC and its affiliated research programs have been supported for over two decades by the National Institute on Aging (Bethesda, Maryland), primarily through grants P01 AG03991 and P50 AG05681. Finally, we dedicate this atlas to our spouses, Louise, Jennifer, Christy, and Lucy, whose support makes our work possible.

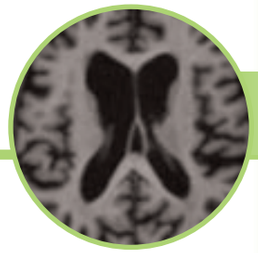
Daniel W McKeel, Jr, MD
Jeffrey M Burns, MD
Thomas M Meuser, PhD
John C Morris, MD

Abbreviations

A4 amyloid beta peptide (synonyms a-beta, Aβ, BAP, 4 kd protein)
AAN American Academy of Neurology
AANP American Association of Neuro-pathologists
ACA anterior cerebral artery
ACTH adrenocorticotropic hormone
AD Alzheimer's disease
ADL activities of daily living
ADRC Alzheimer's Disease Research Center
ADRDA Alzheimer's Disease and Related Disorders Association
AGD argyrophilic grain disease
AHC anterior horn spinal cord
AIDS aquired immunodeficiency syndrome
ALS amyotrophic lateral sclerosis
AON anterior olfactory nucleus
apoE apolipoprotein E
AP anterior pituitary
APP amyloid precursor protein
AS atherosclerosis
aSYN alpha-synuclein
BCRS Brief Cognitive Rating Scale
BN ballooned neuron
BSE bovine spongiform encephalopathy
CA corpora amylacea
CAA cerebral amyloid (a-beta) angiopathy
CADASIL cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CARASIL cerebral autosomal recessive arteriopathy with stroke and ischemic leukoencephalopathy
CBD corticobasal ganglionic degeneration
CC corpus callosum
CDI conformation-dependent immunoassay
CDR Clinical Dementia Rating
CERAD Consortium to Establish a Registry for Alzheimer's Disease
Chr. chromosome
CHS Cardiovascular Health Study
CJD Creutzfeldt-Jakob disease
CLB cortical Lewy body
CNS central nervous system
COW Circle of Willis
CP choroid plexus
CR Congo red
(pm)CSF (postmortem) cerebrospinal fluid
CT computed tomography
DAB diaminobenzidine (stain)
DAT dementia of Alzheimer's type
DBL double barrel lumen
DF dentate fascia
DG Dentate gyrus
DH2O distilled water
DIC differential interference contrast
DLB dementia with Lewy bodies
DLDH dementia lacking distinctive histopathology
DMN dorsal motor nucleus of the vagus nerve (X)
DN dystrophic neurite
DR dorsal raphe
DS Down's syndrome
DSM Diagnostic and Statistical Manual
DSP diffuse senile plaque
EEG electroencephalogram
EM electron microscopy
ERC-II entorhinal cortex layer II stellate cells
FFI fatal familial insomnia
FFPE formalin-fixed paraffin-embedded
fMRI functional magnetic resonance imaging
FTD frontotemporal dementia
FTDP-17 frontotemporal degeneration with parkinsonism linked to chromosome 17
fvFTD frontal variant frontotemporal dementia
GCI glial cell inclusions

GDS Global Deterioration Scale
GFAP glial fibrillary acidic protein
GM gray matter
GP-COG General Practitioner Assessment of Cognition
GSS Gerstmann–Scheinker–Sträussler disease
GVD granulovacuolar degeneration
HD Huntington's disease
HDDD hereditary dysphasic dementia with disinhibition
H&E hematoxylin eosin (stain)
HIPAA Health Insurance Portability and Accountability Act
HIV human immunodeficiency virus
HS hippocampal sclerosis
H-S Hallervorden–Spatz disease
ICA internal carotid artery
ICH intracerebral and cerebellar hemorrhage
IHC immunohistochemistry
IPD idiopathic Parkinson's disease
IQCODE Informant Questionnaire on Cognitive Decline in the Elderly
IRB Institutional Review Board
IVC intraventricular hemorrhage
LB Lewy body
LC locus ceruleus
LCN laminar cortical necrosis
LFB luxol fast blue
LN Lewy neurite
LP lumbar puncture
mab monoclonal antibody
MCA middle cerebral artery
MCI mild cognitive impairment
MID multi-infarct dementia
MMSE Mini-mental State Examination
MND motor neuron disease
MNI motor neuron disease-type inclusions
MRI magnetic resonance imaging
mRNA messenger ribonucleic acid
MS multiple sclerosis
MSA multiple system atrophy
NACC National Alzheimer Coordinating Center, Seattle, WA, USA
NBF neutral buffered formalin
NBIA-I neurodegeneration with brain iron deposition, type 1
NBM nucleus basalis of Meynert
NCL neuronal ceroid lipofuscinosis
NFP neurofibrillary pathology
NFT neurofibrillary tangle
NFTD neurofibrillary tangle dementia
NIA National Institute on Aging
NINCDS-ADRDA National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NNSP non-neuritic senile plaque
NPH normal pressure hydrocephalus
NSP neuritic senile plaque
NT neuropil thread
OPCA olivopontocerebellar ataxia
PAS periodic acid-Schiff
PCA posterior cerebral artery
PD Parkinson's disease
PDD Parkinson's disease dementia
PET positron emission tomography
PHF paired helical filaments
PHF tau hyperphosphorylated tau
PIB Pittsburgh compound-B
PiD Pick's disease
PMI postmortem interval
PML progressive multifocal leukoencephalopathy
PNFA progressive nonfluent aphasia
PNFD progressive nonfluent dysphasia
PP perforant pathway
PS1(2) presenilin 1(2)
PSFF paraffin sections of formalin fixed
PSP progressive supranuclear palsy
RBC red blood cell
REM rapid eye movement
RS Richardson's syndrome
RT real-time polymerase chain reaction
SAH subarachnoid hemorrhage
SBT Short Blessed Test
sCJD sporadic Creutzfeldt–Jakob disease
SD semantic dementia
SDH subdural hemorrhage
SGL supragranular layer
sIPD spontaneous idiopathic Parkinson's disease
SLE systemic lupus erythematosus
SN substantia nigra
SOD superoxide dismutase
SND striatonigral dementia
SP senile plaque
SPECT single photon emission computed tomography
STG superior temporal gyrus
TIA transient ischemic attack
TPA tissue plasminogen activator
TSE transmissible spongiform encephalopathy

TSH thyroid stimulating hormone
TSP total senile plaques
TTP thrombotic thrombocytopenic purpura
VaD vascular dementia
vCJD variant Creutzfeldt–Jakob disease
VH visual hallucinations
VPD vascular parkinsonism
V-R Virchow–Robins (perivascular spaces)
VTA ventral tegmental area
WAIS Wechsler Adult Intelligence Scale
WM white matter
WMI white matter infarct
WML white matter lesion



Chapter 1

Cognitive aging and dementia: an overview

Introduction

In 1907 Alois Alzheimer first described the clinical and pathologic features of the disease that now bears his name. Professor Alzheimer was among the first to correlate higher order cognitive dysfunction with changes in brain structure. Since then, the science of neuropathology has played an important role in the nosology of dementia, as Professor Alzheimer predicted:

> 'It is clear that there exist many more mental diseases than our textbooks indicate. In many such cases, a further histological examination must be effected to determine the characteristics of each single case. We must reach the stage in which the vast well-known disease groups must be subdivided into many smaller groups, each with its own clinical and anatomical characteristics' (translation by Bick & Amaducci, 1989).

Our understanding of disorders of higher cognitive function has advanced considerably in the last century, largely as a result of clinicopathologic studies such as Professor Alzheimer's. While molecular genetics and DNA analysis are now contributing importantly to disease classification, clinical and pathologic classifications will remain essential to interpreting the relationship of genotype and phenotype (Morris, 2000).

Dementia

Dementia is a clinical syndrome of acquired cognitive impairment produced by brain dysfunction. Dementia represents a decline from a higher level of cognitive function such that accustomed activities are accomplished less well or relinquished altogether. The American Academy of Neurology recommends the routine use of the Diagnostic and Statistical Manual (DSM) criteria for diagnosing dementia, which has been shown to be a reliable indicator of the presence of dementia (*Table 1.1*).

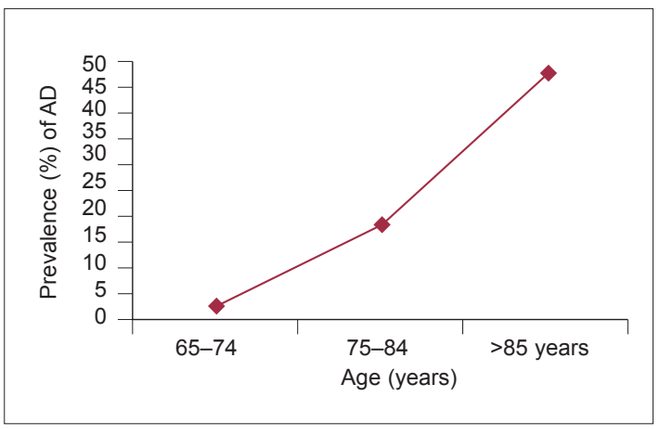
Dementia is a common disorder in older adults, involving as many as 10% of those over the age of 65 years. Increased life expectancy in the US and other developed countries has fueled an unprecedented growth in the elderly population

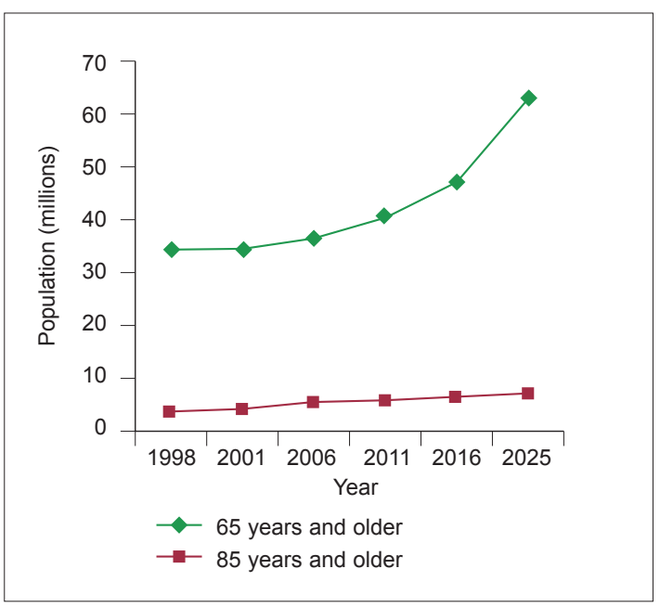
Table 1.1 Definition of dementia: DSM IV

- Impairment in short- and long-term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of higher cortical function, or personality change
- The disturbance is severe enough to interfere significantly with work or usual social activities or relationships with others

(American Psychiatric Association, 1994)

that is leading to dramatic increases in the incidence of dementia. The prevalence of the most common cause of dementia, Alzheimer's disease (AD), doubles every 5 years after the age of 65 years, and reaches nearly 50% after age 85 years (Evans *et al.*, 1989) (**1.1**). Currently, there are an estimated 4.5 million people in the US with AD and 20 million worldwide (World Health Organization); the incidence of AD has been projected to nearly triple in the US over the next 50 years (Hebert *et al.*, 2001) (**1.2**). The annual treatment costs of AD in the US are estimated at $100 billion with the cost to government agencies rising rapidly: Medicare spending on AD will grow to $49.3 billion (a 54% increase over the costs in 2000), and Medicaid spending will grow to $33 billion (an 80% increase over costs in 2000) (Prigerson, 2003).





Brain aging and dementia

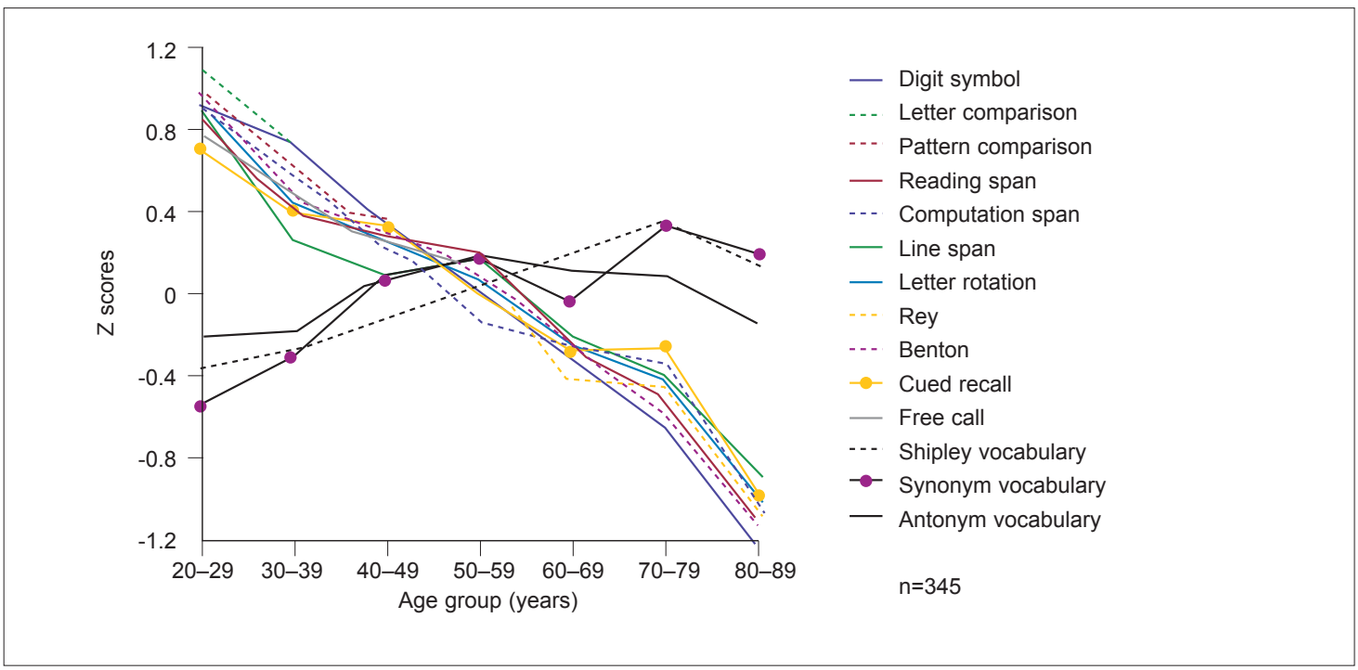
It is well accepted that advancing age is associated with cognitive changes. When compared directly with younger subjects, older subjects tend to process information at a slower rate, manipulate and store information (working memory) less efficiently, and have declines in free-recall of word lists. On the other hand, cognitive declines with age are not universal to all types of cognition. For instance, crystallized intelligence (such as measures of knowledge and vocabulary) is stable across the lifespan (Park *et al.*, 2001) (**1.3**). Additionally, the magnitude of the deficits observed with age generally are small and do not appear to impair overall function appreciably or the ability to carry out activities of daily living (Rubin *et al.*, 1993).

The aging brain is associated with structural changes in even the healthiest individuals that may underlie some of the cognitive changes that are observed with age. Normal aging is associated with a slow and steady loss of brain tissue beginning in early adulthood and continuing over the lifespan (**1.4**) (Jernigan *et al.*, 2001; Bartzokis *et al.*, 2003; Fotenos *et al.*, 2005). White matter myelination continues into the fourth decade (Hildebrand *et al.*, 1993; Bartzokis *et al.*, 2001) but declines thereafter, with the occurrence of

1.1 Prevalence of Alzheimer's disease in an aging population. Prevalence increases dramatically with age and approaches 50% of those over 85 years old. (Adapted from Evans *et al.*, 1989.)

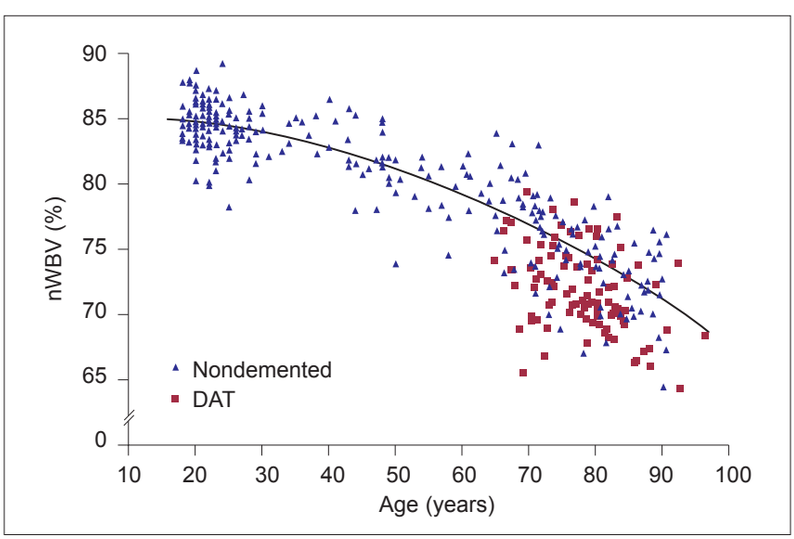
1.2 Population estimate for older adults in the US. The US Census Bureau (2000) projects the population of 65 years will increase dramatically by the year 2025 (middle series estimates). The 85 years and older group is the fastest growing segment of the population.

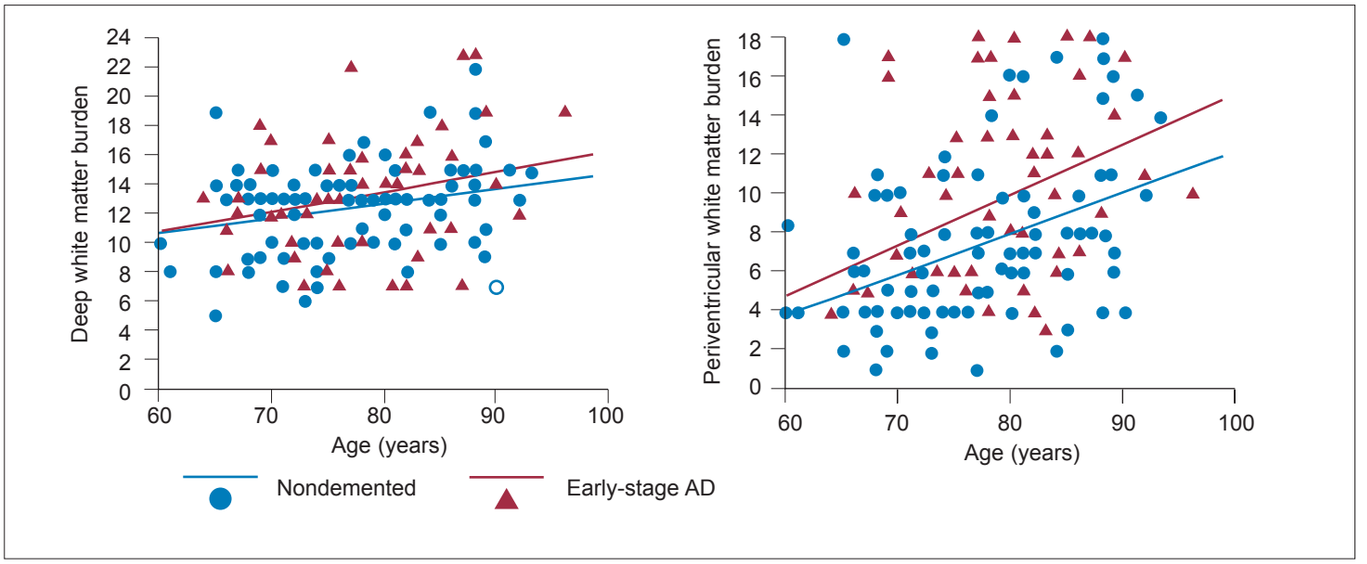
normal age-related breakdown in myelin (**1.5**) and the accumulation of changes in the white matter on magnetic resonance imaging (MRI) in older adults (**1.6**) (Longstreth *et al.*, 1996). Subclinical or 'silent' brain infarcts are present in up to 33% of nondemented older adults (Longstreth *et al.*, 1996; Vermeer *et al.*, 2002) and increase in prevalence with increasing age. These age-related brain changes are likely to play a role in the changes in cognition that occur



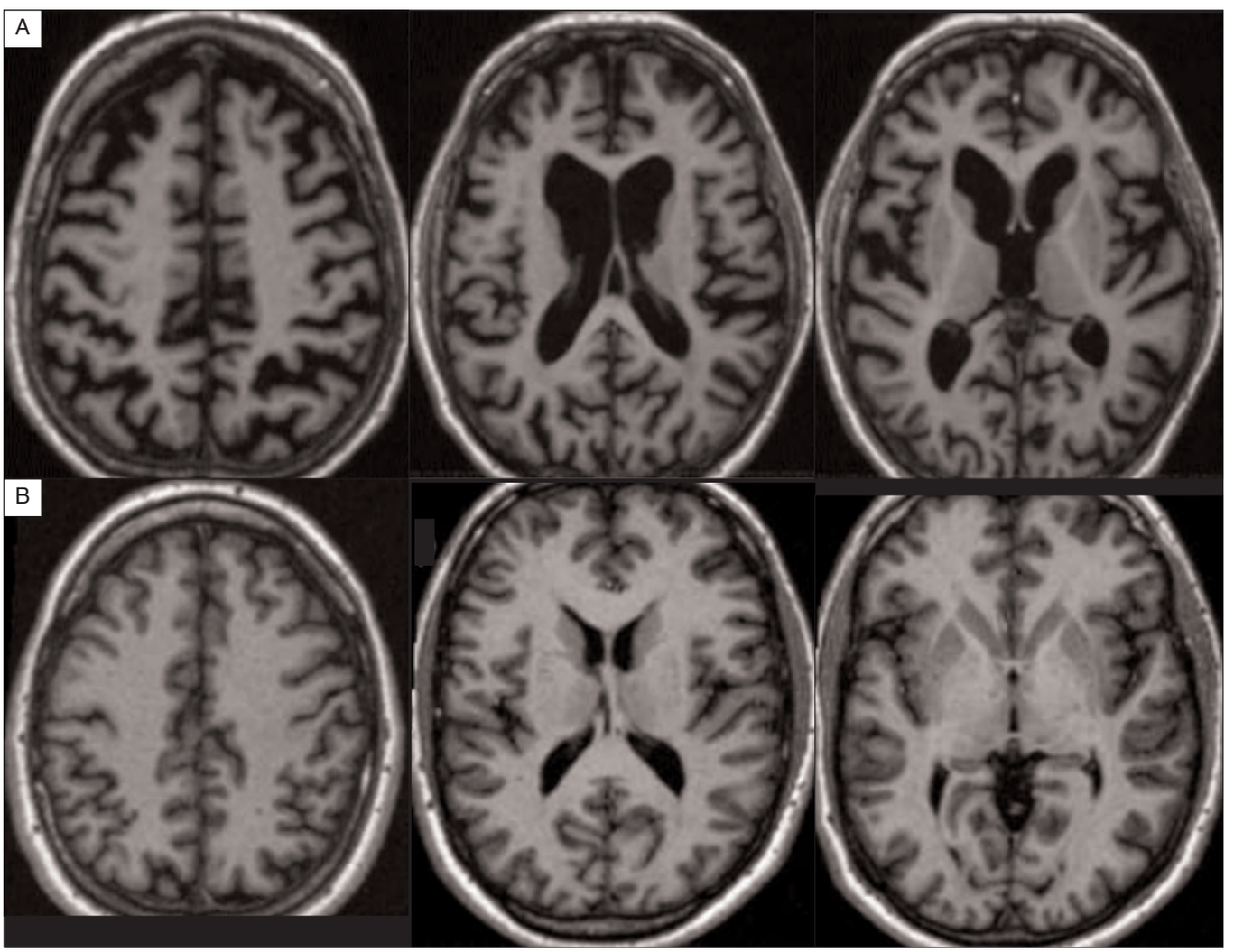
1.3 Cognitive decline with age. Some aspects of cognition, such as processing speed and working memory, are consistently reported to decline with age while others such as vocabulary, remain stable. Methodologic issues complicate these findings as longitudinal studies (following one individual over time) show less or no decline in cognition than cross-sectional studies (groups of individuals studied at one point in time). (Adapted from Park *et al.*, 2001.)

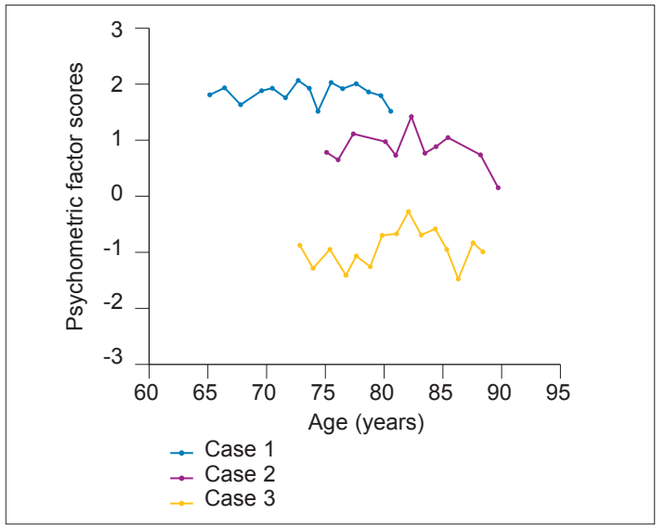
1.4 Cross-sectional plot of brain volume across the adult lifespan. Normal aging is associated in a slow and steady loss of brain tissue beginning in the seventh decade and extending over the lifespan. DAT: dementia of Alzheimer type; nWBV: normalized whole brain volume. (Adapted from Fotenos *et al.*, 2005.)



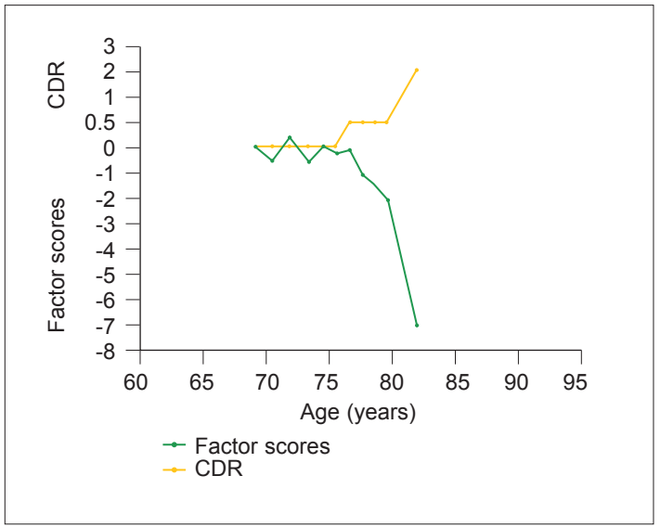


1.5 The burden of white matter lesions increases with age in individuals with early stage AD and healthy controls. (Adapted from Burns *et al*., 2005.)





1.7 Stable cognitive performance with age in three nondemented controls. Factor score is an index of general cognitive performance generated from a battery of neuropsychologic tests. The large majority of a group of nondemented subjects followed for up to 15 years showed no decline in a standardized score of general cognitive performance.



1.8 Cognitive decline in dementia. An abrupt decline in psychometric performance (green) occurs in this individual once subtle cognitive decline is detected (Clinical Dementia Rating (CDR) of 0.5, yellow). Stable cognitive performance is generally maintained up until the onset of a dementing illness, at which time a steep decline in performance occurs. Factor score is an index of cognitive performance. (Adapted from Rubin *et al*., 1998.)

with advancing age. Additionally, there is a complex relationship between age-related brain changes and AD pathology. For instance, less AD neuropathology is required to produce clinically apparent dementia in the setting of cerebrovascular disease (Snowdon *et al.*, 1997; Esiri *et al.*, 1999; Zekry *et al.*, 2002). Thus, age-related brain changes are likely to contribute to the cognitive changes seen in healthy aging but also appear to influence the expression of AD in the aging population.

A central but unresolved issue is determining which cognitive changes can be accepted as part of normal aging. The mildest cognitive changes ascribed to early AD overlap considerably with cognitive performance in healthy aging individuals (Galasko *et al.*, 1990; Morris *et al.*, 1991; Devanand *et al.*, 1997; Herlitz *et al.*, 1997). This has, in part, prompted the consideration that aging and AD are part of the same spectrum (Ebly *et al.*, 1994), with cognitive decline and 'senility' suggested to be an inevitable result of the aging process. In fact, when strict criteria are employed to exclude even minimally demented individuals from longitudinal studies of cognitively normal elderly, psychometric performance is shown to be surprisingly stable (Howieson *et al.*, 1997; Rubin *et al.*, 1998; Storandt *et al.*, 2002). Thus, substantial cognitive decline need not be a part of truly healthy brain aging (Crystal *et al.*, 1988; Morris *et al.*, 1993; Howieson *et al.*, 1997; Rubin *et al.*, 1998; Haan *et al.*, 1999), suggesting that AD is not inevitable with age.

Clinical studies support a distinction between aging and AD. Cognitively healthy elderly individuals maintain generally stable cognitive performance when followed longitudinally over time (**1.7**). At dementia onset, however, a steep decline in cognitive performance occurs, suggesting the onset of disease is distinct from the aging process (**1.8**). While subtle changes can be expected with age, cognitive decline interfering even mildly with the ability to perform daily functions appears to be a marker of disease.

1.6 (Opposite.) Brain atrophy with age. Global atrophy is apparent in the brain of a 90-year-old nondemented man (**A**). The ventricles are significantly enlarged with prominent sulci. For comparison, a 39-year-old nondemented man (**B**) demonstrating smaller ventricles, fuller white matter, and less prominent sulci. (Courtesy of Randy L Buckner.)

Alzheimer's disease and mild cognitive impairment

AD represents the most common cause of dementia, accounting for 55–70% of cases of dementia. AD is often accompanied by other age-related disorders. Vascular lesions and Parkinson's disease most commonly coexist with AD, each occurring in about 25% of AD cases. 'Pure' AD accounts for about 50–60% of clinically diagnosed cases of dementia. These concomitant disorders contribute to the expression of AD, as the histopathologic burden of AD lesions for a given level of dementia severity is lower when AD is mixed with other disorders (Nagy *et al.*, 1997; Snowdon *et al.*, 1997; Berg *et al.*, 1998). Given heterogeneity of clinical features and common pathologic overlap, the true occurrence of the non-AD dementias is difficult to ascertain. Dementia with Lewy bodies, vascular dementia, and the frontotemporal dementias are considered to be the most common forms of non-AD dementias (*Tables 1.2*, *1.3*).

The term mild cognitive impairment (MCI) is one of many introduced to characterize the boundary of aging and dementia (Kral, 1962; Crook & Bartus, 1986; Flicker *et al.*, 1991; Levy, 1994; Graham *et al.*, 1997; Petersen *et al.*, 1999, 2001a). MCI was specifically intended to capture those patients destined to develop dementia (Flicker *et al.*, 1991). The onset of symptomatic AD is insidious and patients with AD almost always progress through a period of subtle cognitive impairments that do not interfere importantly with their daily functioning. Thus, the concept of MCI includes individuals in this prodromal stage that occurs prior to the diagnosis of overt dementia. Broadly defined, MCI includes (1) evidence of cognitive impairment; (2) preservation of general cognition and functional abilities; and (3) absence of diagnosed dementia. Prevalence estimates for MCI demonstrate considerable variability, ranging from 2.8% to as high as 23.4% (Ebly *et al.*, 1995; Ritchie *et al.*, 2001; Unverzagt *et al.*, 2001; Larrieu *et al.*, 2002; Lopez *et al.*, 2003). Estimates of the risk of 'conversion' from MCI to AD are also widely variable, ranging from 3.7% per year (Ritchie *et al.*, 2001) to 25% in selected samples (Flicker *et al.*, 1991; Dawe *et al.*, 1992). The wide variability in MCI prevalence and estimates of the risk for developing overt AD is due to differences in MCI definitions, study design (retrospective vs. prospective), and the sample studied (referral-based vs. population-based) (Luis *et al.*, 2003).

While MCI captures individuals with the earliest changes of AD or other forms of dementia (i.e. vascular dementia, frontotemporal dementia, dementia with Lewy bodies), it encompasses many different conditions including static cognitive impairment, the 'worried well', and reversible forms of cognitive dysfunction such as those related to depression or medical illnesses. In general, however, it seems clear that individuals with MCI progress to overt AD at a rate far above the baseline dementia incidence rate. Although the concept of MCI is not without controversy, it has served to focus attention on the delineation of the earliest symptoms of AD from the change of normal cognitive aging.

Table 1.2 Differential diagnosis of cognitive decline

- Neurodegenerative dementia (see *Table 1.3*)
- Cerebrovascular disorders:
  - Vascular dementia
  - Binswanger's disease
- Infectious disorders:
  - Chronic meningitis
  - Encephalitis:
    - Human immunodeficiency virus
    - Lyme disease
  - Progressive multifocal leukoencephalopathy
  - Neurosyphilis
  - Whipple's disease
- Toxic/metabolic encephalopathies
  - Drugs/medications
  - Endocrine: thyroid, parathyroid:
    - Nutritional: B_{12} and thiamine deficiencies
    - Fluid and electrolyte abnormalities
    - Hypoglycemia
    - Other: carbon monoxide, heavy metals (lead, mercury, arsenic, thallium)
- Inflammatory:
  - Vasculitis:
    - Primary central nervous system vasculitis
    - Systemic vasculitides:
      - Systemic lupus erythematosus
      - Polyarteritis nodosa
      - Wegener's granulomatosus
      - Churg–Strauss syndrome
      - Sarcoidosis
- Demyelinating:
  - Multiple sclerosis
- Neoplastic:
  - Direct effects of primary and metastatic disease
  - Paraneoplastic syndromes
- Hydrocephalus
- Affective disorders (depression)
- Neurogenetic disorders:
  - Spinocerebellar ataxias
  - Dentatorubral-pallidoluysian atrophy
  - Hallervorden–Spatz disease
  - Gangliosidoses
  - Adult neuronal ceroid lipofuscinosis (Kuf's disease)
  - Mitochondrial encephalopathies
  - Porphyrias
  - Wilson's disease

Table 1.3 Neurodegenerative dementias

- Alzheimer's disease
- Dementia with Lewy bodies
- Vascular dementia
- Frontotemporal lobar degeneration:
  - Frontotemporal dementia
  - Semantic dementia
  - Progressive nonfluent aphasia
- Progressive supranuclear palsy
- Corticobasal degeneration
- Parkinson's disease with dementia
- Multiple system atrophy
- Huntington's disease
- Prion disorders:
  - Creutzfeldt–Jakob disease
  - Fatal familial insomnia
  - Gerstmann–Sträussler–Scheinker disease

Diagnosis and evaluation of dementing disorders

The key information for diagnosing dementia comes primarily from the clinical information, resting largely on determining whether cognitive decline is present to such a degree as to interfere with function in usual activities. The 2001 American Academy of Neurology (AAN) practice parameter on the diagnosis of dementia recommended the routine use of the DSM criteria (Knopman *et al.*, 2001b). The criteria's key principles include (1) cognitive decline; and (2) interference with functioning as the ultimate validation of the presence of dementia (*Table 1.4*). Assessing whether these criteria are met involves (1) evaluating the presenting problem; (2) obtaining information from someone who knows the patient well (i.e. obtaining an informant-based history); (3) physical and neurologic examinations; and (4) evaluation of the cognitive, behavioral, and functional status of the patient. Dementia remains a clinical diagnosis and no test replaces an assessment by an experienced physician.

Table 1.4 Clinical hallmarks of dementia

- Gradual onset
- Progressive decline
- Memory loss
- Other cognitive domains impaired
- Interferes with function

Table 1.5 Features suggestive of other dementing illness

- Parkinsonism → dementia with Lewy bodies, corticobasal degeneration
- Language:
  - Naming impairment → progressive nonfluent aphasia
  - Comprehension impairment → semantic dementia
- Apraxia → corticobasal degeneration
- Myoclonus → prion disease (Creutzfeldt–Jakob disease)

Importance of an informant-based history

Establishing a history of a significant cognitive decline must be individualized because each individual's usual activities vary according to native intelligence and their educational and occupational experiences. It is therefore important to gather information about cognitive changes from someone who knows the patient well, such as the spouse or a family member. The memory loss of early-stage AD is generally well compensated. Individuals may continue to perform independently in the community and symptoms may not be readily apparent in casual contact with others. Discussing cognitive changes with an attentive family member, relative, or friend is essential in making a confident diagnosis using their descriptions of cognitive changes to establish whether cognitive changes are interfering even mildly with the patient's usual function. The perceptions of a knowledgeable informant are sensitive and reliable for detecting early dementia (McGlone *et al.*, 1990; Koss *et al.*, 1993; Tierney *et al.*, 1996; Jorm, 1997; Carr *et al.*, 2000). Additionally, self-reported memory complaints do not correlate well with actual cognitive performance and are not a strong predictor of the development of dementia (Bolla *et al.*, 1991; Flicker *et al.*, 1993). On the other hand, these self-reported complaints should not necessarily be dismissed as benign as patients with early AD often retain some insight into their cognitive difficulties.

Neurologic examination

In mild and even moderate AD, focal neurologic abnormalities are infrequent and the neurologic examination is performed primarily to evaluate for any signs suggestive of another dementing illness (*Table 1.5*). The neurologic examination should therefore be focused on evaluating for the presence of focal upper motor neuron signs, extrapyramidal signs, and prominent aphasia and apraxia.

Mild impairments in language and praxis are commonly encountered in AD, although memory loss remains the prominent symptom. Language impairments often begin with mild word-finding difficulties, manifested as circumlocutions (substituting the desired word with a description or series of shorter words) and halting speech. Unexplained language impairments with relative sparing of memory may indicate the presence of a variant of

frontotemporal lobar degeneration such as nonfluent progressive aphasia or semantic dementia.

Apraxia, a disorder of skilled movement despite intact strength, sensation, and coordination, will develop as typical AD progresses but is not a prominent early manifestation. Apraxia in mild AD patients is commonly characterized as substitution of the individual's hand as object, for instance using their fist to represent a hammer rather than grasping an imaginary hammer. Severe apraxia, often unilateral, may indicate corticobasal degeneration.

Focal neurologic deficits such as mild hemiparesis, unilateral visual field deficit, or Babinski sign may indicate the presence of significant vascular disease which commonly coexists with AD, and may play a role in the symptomatic expression of AD (Snowdon *et al.*, 1997). The presence of increased tone and a Parkinsonian gait early in the course may indicate dementia with Lewy bodies or Parkinson's dementia. Extrapyramidal signs are common in advanced AD but are generally not prominent early in the course; prominent unilateral extrapyramidal signs may indicate corticobasal degeneration. Prominent myoclonus may indicate Creutzfeldt–Jakob disease, especially if accompanying a rapidly progressive dementing illness, although myoclonus can also be encountered in the late stages of AD.

Laboratory and radiological evaluation

Structural neuroimaging is recommended in the form of either MRI or noncontrast computed tomography (CT). The basis of this recommendation is the evidence that up to 5% of patients with dementia have a clinically significant structural lesion that would not have been predicted based on the history or examination (Chui & Zhang, 1997). These potential lesions include brain neoplasms, subdural hematomas, or normal pressure hydrocephalus. However, fully reversible dementia due to unsuspected causes is rare. The AAN practice paramenter reported insufficient evidence to recommend single photon emission computed tomography (SPECT) or positron emission tomography (PET) in the routine evaluation of dementia patients. Additionally, PET and SPECT imaging have not been shown to be cost-effective for dementia diagnosis (McMahon *et al.*, 2000).

Depression, B_{12} deficiency, and hypothyroidism are common co-morbidities in patients with suspected dementia, and screening for these treatable disorders is recommended (*Table 1.6*) (Knopman *et al.*, 2001). Depression coexists with AD in up to 12% of demented patients (Forsell and Winblad, 1998), and a few reports have attributed dementia to B_{12} deficiency and hypothyroidism (Clarfield, 1988). In most individuals, treatment of these disorders is unlikely to reverse cognitive deficits completely, and cognitive improvement in demented patients with B_{12} and thyroid replacement are equivocal (Knopman *et al.*, 2001a). Nevertheless, the high frequency of these co-morbidities and the potential for amelioration of cognitive symptoms necessitates screening. Routine screening for syphilis is no longer recommended, a change from the 1994 practice parameter (American Academy of Neurology/Quality Standards Subcommittee, 1994) unless syphilis risk factors or evidence of infection exists.

Table 1.6 Basic laboratory assessment for cognitive impairment

- Neuroimaging:
  - CT or MRI
- Laboratory:
  - Thyroid
  - Vitamin B_{12}
  - Syphilis (only if clinically indicated)

Psychometric/mental status testing

Mental status tests should be used primarily to confirm the presence of cognitive deficits and not as a method of diagnosis. Mental status tests cannot, certainly at the initial evaluation, indicate whether the individual has declined from previous levels of cognitive abilities nor determine the presence of impairment sufficient to interfere with accustomed activities. This information must be collected from the informant interview. Testing is useful in demonstrating a pattern of deficits consistent with an AD pattern (primary deficits in memory and executive function) and to monitor dementia progression over time through serial testing. Over-reliance on cognitive test performance in

addition to failure to incorporate an informant's observations about an individual's cognitive function in relation to past abilities results in the under-recognition of mild AD.

The determination of normal and abnormal performance on psychometric tests uses arbitrary cutoff points and standard deviations for a group means of memory performance. These means are not always applicable to an individual. Cognitive tests, such as the Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) are influenced by age, education (Doraiswamy *et al.*, 1995), race (Manly *et al.*, 1998), and gender, and show large measurement error (*Table 1.7*). These factors often make cognitive tests insensitive to early-stage AD (Galasko *et al.*, 1990; Devanand *et al.*, 1997; Herlitz *et al.*, 1997). The performance of nondemented aging and very mild and mild AD individuals on widely used cognitive scales such as the MMSE and the Blessed Scale-cognitive portion (Blessed *et al.*, 1968) show considerable overlap between the groups. This suggests that over-reliance on neuropsychologic tests would exclude some individuals experiencing interference with their usual functions who are still performing within the arbitrary range of normal.

Summary

The key information for diagnosing dementia comes primarily from the clinical assessment. In establishing a diagnosis, clinicians should obtain a history from someone who knows the patient well as the perceptions of a knowledgeable informant are sensitive and reliable for detecting early dementia (McGlone *et al.*, 1990; Koss *et al.*, 1993; Tierney *et al.*, 1996; Jorm,1997; Carr *et al.*, 2000). While brain aging is associated with structural and functional changes, cognitive changes seen normally with age are generally mild and should not be expected to interfere, even mildly, with an individual's accustomed activities of daily living.

There is currently a great interest in the potential utility of biomarkers, neuroimaging, and genetics in augmenting, or even replacing, the clinical diagnosis of dementing disorders. Clinical methods, however, remain the gold standard for the antemortem diagnosis of dementia and AD. Additionally, clinical and pathologic classifications will remain the backbone of interpreting these methods and in advancing our understanding of the complex interplay between genotype and phenotype.

Table 1.7 Selective cognitive instruments used in detection of dementia

Instrument (cutoff)	*Sensitivity (%)*	*Specificity (%)*
MMSE (<24) (Kukull *et al.*, 1994)	63	96
MMSE (bottom 10%) (Ganguli *et al.*, 1993)	49	92
MMSE (decline of 4 points)/1–4 years (Tangalos *et al.*, 1996)	82	99
Seven-minute screen (Solomon *et al.*, 1998)	92	96
Clock drawing test (Shulman, 2000)	85	85
CDR (Juva *et al.*, 1995)	92	94
IQCODE (Fuh *et al.*, 1995)	89	88

CDR: Clinical Dementia Rating Scale; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly.
(From Petersen *et al.*, 2001b)

References

American Academy of Neurology/Quality Standards Subcommittee (1994). Practice parameter for diagnosis and evaluation of dementia. *Neurology* **44**:2203–2206.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders.* Washington, DC: American Psychiatric Association.

Bartzokis G, Beckson M, Lu PH, *et al.* (2001). Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Arch. Gen. Psychiatry* **58**:461–465.

Bartzokis G, Cummings JL, Sultzer D, *et al.* (2003). White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study. *Arch. Neurol.* **60**:393–398.

Berg L, McKeel DW Jr., Miller JP, *et al.* (1998). Clinicopathologic studies in cognitively healthy aging and Alzheimer disease: relation of histological markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch. Neurol.* **55**:326–335.

Bick KL, Amaducci L (1989). *The Early Story of Alzheimer's Disease*. Liviana Press, Padova.

Blessed G, Tomlinson BE, Roth M (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of the elderly subjects. *Br. J. Psychiatry* **114**:797–811.

Bolla KI, Lindgren KN, Bonaccorsy C, *et al.* (1991). Memory complaints in older adults: fact or fiction? *Arch. Neurol.* **48**:61–64.

Burns JM, Church JA, Johnson DK, *et al.* (2005). White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease. *Arch Neurol* **62**(12):1870–1876.

Carr DB, Gray S, Baty J, *et al.* (2000). The value of informant vs. individual's complaints of memory impairment in early dementia. *Neurology* **55**:1724–1726.

Chui H, Zhang Q (1997). Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's practice parameters. *Neurology* **49**:925–935.

Clarfield AM (1988). The reversible dementias: do they reverse? *Ann. Intern. Med.* **109**:476–486.

Crook TH, Bartus RT (1986). Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change; Report of a National Institute of Mental Health work group. *Dev. Neuropsychol.* **2**:261–276.

Crystal H, Dickson D, Fuld P, *et al.* (1988). Clinico-pathologic studies in dementia: nondemented subjects with pathologically confirmed Alzheimer's disease. *Neurology* **38**:1682–1687.

Dawe B, Procter A, Philpot M (1992). Concepts of mild memory impairment in the elderly and their relationship to dementia: a review. *Int. J. Geriatr. Psychiatry* **7**:473–479.

Devanand DP, Folz M, Gorlyn M, *et al.* (1997). Questionable dementia: clinical course and predictors of outcome. *J. Am. Geriatr. Soc*. **45**:321–328.

Doraiswamy PM, Krishen A, Stallone F, *et al.* (1995). Cognitive performance on the Alzheimer's disease assessment scale: effect of education. *Neurology* **45**:1980–1984.

Ebly EM, Hogan DB, Parhad IM (1995). Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. *Arch. Neurol.* **52**:612–619.

Ebly EM, Parhad IM, Hogan DB, *et al.* (1994). Prevalence and types of dementia in the very old. Results from the Canadian Study of Health and Aging. *Neurology* **44**:1593–1600.

Esiri MM, Nagy Z, Smith MZ, *et al.* (1999). Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet* **354**:919–920.

Evans DA, Funkenstein HH, Albert MS, *et al.* (1989). Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. *JAMA* **262**:2551–2556.

Flicker C, Ferris SH, Reisberg B (1991). Mild cognitive impairment in the elderly: predictors of dementia. *Neurology* **41**:1006–1009.

Flicker C, Ferris SH, Reisberg B (1993). A longitudinal study of cognitive function in elderly persons with subjective memory complaints. *J. Am. Geriatr. Soc.* **41**:1029–1032.

Folstein MF, Folstein SE, McHugh PR (1975). Mini-mental state: a practical method for grading the cognitive state of patients for the clinicians. *J. Psychiatr. Res.* **12**:189–198.

Forsell Y, Winblad B (1998). Major depression in a population of demented and nondemented older people: prevalence and correlates. *J. Am. Geriatr. Soc.* **46**:27–30.

Fotenos AF, Snyder AZ, Girton LE, *et al.* (2005). Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology* **64**:1032–1039.

Fuh JL, Teng EL, Lin KN, *et al.* (1995). The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening tool for dementia for a predominantly illiterate Chinese population. *Neurology* **45**:92–96.

Galasko D, Klauber MR, Hofstetter R (1990). The Mini-mental state examination in the early diagnosis of Alzheimer's disease. *Arch. Neurol.* **47**:49–52.

Ganguli M, Belle S, Ratcliff G, *et al.* (1993). Sensitivity and specificity for dementia of population-based criteria for cognitive impairment: the MoVIES project. *J. Gerontol.* **48**:M152–M161.

Graham JE, Rockwood K, Beattie LB, *et al.* (1997). Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* **349**:1793–1796.

Haan MN, Shemanki L, Jagust WJ, *et al.* (1999). The role of APOE e4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA* **282**:40–46.

Hebert LE, Beckett LA, Scherr PA, *et al.* (2001). Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. *Alz. Dis. Assoc. Disord.* **15**:169–173.

Herlitz A, Small BJ, Fratiglioni L, *et al.* (1997). Detection of mild dementia in community surveys. *Arch. Neurol.* **54**:319–324.

Hildebrand C, Remahl S, Persson H, *et al.* (1993). Myelinated nerve fibres in the CNS. *Prog. Neurobiol.* **40**:319–384.

Howieson DB, Dame A, Camicioli R, *et al.* (1997). Cognitive markers preceding Alzheimer's dementia in the healthy oldest old. *J. Am. Geriatr. Soc.* **45**:584–589.

Jernigan TL, Archibald SL, Fennema-Notestine C, *et al.* (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging* **22**:581–594.

Jorm AF (1997). Methods of screening for dementia: a meta-analysis of studies comparing an informant questionnaire with a brief cognitive test. *Alz. Dis. Assoc. Disord.* **11**:158–162.

Juva K, Sulkava R, Erkinjuntti T, *et al.* (1995). Usefulness of the Clinical Dementia Rating scale in screening for dementia. *Int. Psychogeriatr.* **7**:17–24.

Knopman DS, DeKosky ST, Cummings JL, *et al.* (2001). Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **56**:1143–1153.

Koss E, Patterson MB, Ownby R, *et al.* (1993). Memory evaluation in Alzheimer's disease: caregivers' appraisals and objective testing. *Arch. Neurol.* **50**:92–97.

Kral VA (1962). Senescent forgetfulness: benign and malignant. *Can. Med. Assoc. J.* **86**:257–260.

Kukull WA, Larson EB, Teri L, *et al.* (1994). The mini-mental state examination score and the clinical diagnosis of dementia. *J. Clin. Epidemiol.* **47**:1061–1067.

Larrieu S, Letenneur L, Orgogozo JM, *et al.* (2002). Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology* **59**:1594-1599.

Levy R (1994). Aging-associated cognitive decline. *Int. Psychogeriatr.* **6**:63-68.

Longstreth WT, Manolio TA, Arnold A, *et al.* (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: The Cardiovascular Health Study. *Stroke* **27**:1274–1282.

Lopez OL, Jagust WJ, Dulberg C, *et al.* (2003). Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: Part 2. *Arch. Neurol.* **60**:1394–1399.

Luis CA, Loewenstein DA, Acevedo A, *et al.* (2003). Mild cognitive impairment: directions for future research. *Neurology* **61**:438–444.

Manly JJ, Jacobs DM, Sano M, *et al.* (1998). Cognitive test performance among nondemented elderly African Americans and whites. *Neurology* **50**:1238–1245.

McGlone J, Gupta S, Humphrey D, *et al.* (1990). Screening for early dementia using memory complaints from patients and relatives. *Arch. Neurol.* **47**:1189–1193.

McMahon PM, Araki SS, Neumann PJ, *et al.* (2000). Cost-effectiveness of functional imaging tests in the diagnosis of Alzheimer disease. *Radiology* **217**:58–68.

Morris JC (2000). Nosology of dementia. In: *Neurologic Clinics*. ST DeKosky (ed). W.B. Saunders Company, Philadelphia, pp. 773–788.

Morris JC, Edland S, Clark C, *et al.* (1993). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. *Neurology* **43**:2457–2465.

Morris JC, McKeel DW Jr., Storandt M, *et al.* (1991). Very mild Alzheimer's disease: informant-based clinical, psychometric, and pathological distinction from normal aging. *Neurology* **41**:469-478.

Nagy Z, Esiri MM, Jobst KA, *et al.* (1997). The effects of additional pathology on the cognitive deficit in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* **56**:165–170.

Park DC, Plk TA, Mikels, *et al.* (2001). Cerebral aging: brain and behavioral models of cognitive function. *Dialog. Clin. Neurosci*. **3**:151–165.

Petersen RC, Smith GE, Waring SC *et al.* (1999). Mild cognitive impairment – clinical characterization and outcome. *Arch. Neurol.* **56**(3):303–3-8.

Petersen RC, Doody R, Kurz A, *et al.* (2001a) Current concepts in mild cognitive impairment. *Arch. Neurol.* **58**(12):1985–1992.

Petersen RC, Stevens JC, Ganguli M, *et al.* (2001b). Practice parameter: Early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **56**:1133–1142.

Prigerson HG (2003). Costs to society of family caregiving for patients with end-stage Alzheimer's disease. *N. Engl. J. Med.* **349**:1891–1892.

Ritchie K, Artero S, Touchon J (2001). Classification criteria for mild cognitive impairment. A population-based validation study. *Neurology* **56**:37–42.

Rubin EH, Storandt M, Miller JP, *et al.* (1993). Influence of age on clinical and psychometric assessment of subjects with very mild or mild dementia of the Alzheimer type. *Arch. Neurol.* **50**:380–383.

Rubin EH, Storandt M, Miller JP, *et al.* (1998). A prospective study of cognitive function and onset of dementia in cognitively healthy elders. *Arch. Neurol.* **55**:395–401.

Shulman K (2000). Clock-drawing: is it the ideal cognitive screening test? *Int. J. Geriatr. Psychiatry* **15**:548–561.

Snowdon DA, Greiner LH, Mortimer JA, *et al.* (1997). Brain infarction and the clinical expression of Alzheimer disease. *JAMA* **277**:813–817.

Solomon PR, Hirschoff A, Kelly B, *et al.* (1998) A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. *Arch. Neurol*. **55**:349–355.

Storandt M, Grant EA, Miller JP, *et al.* (2002). Rates of progression in mild cognitive impairment and early Alzheimer's disease. *Neurology* **59**:1034–1041.

Tangalos EG, Smith GE, Ivnik RJ, *et al.* (1996) The Mini-Mental State Examination in general medical practice: clinical utility and acceptance. *Mayo Clin. Proc.* **71**:829–837.

Tierney MC, Szalai JP, Snow WG, *et al.* (1996). The prediction of Alzheimer disease. *Arch. Neurol.* **53**:423–427.

Unverzagt FW, Gao S, Baiyewu O, *et al.* (2001). Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging. *Neurology* **57**:1655–1662.

Vermeer SE, Koudstaal PJ, Oudkerk M, *et al.* (2002). Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* **33**:21–25.

Zekry D, Duyckaerts C, Moulias R, *et al.* (2002). Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. *Acta Neuropathol. (Berl.)* **103**:481–487.