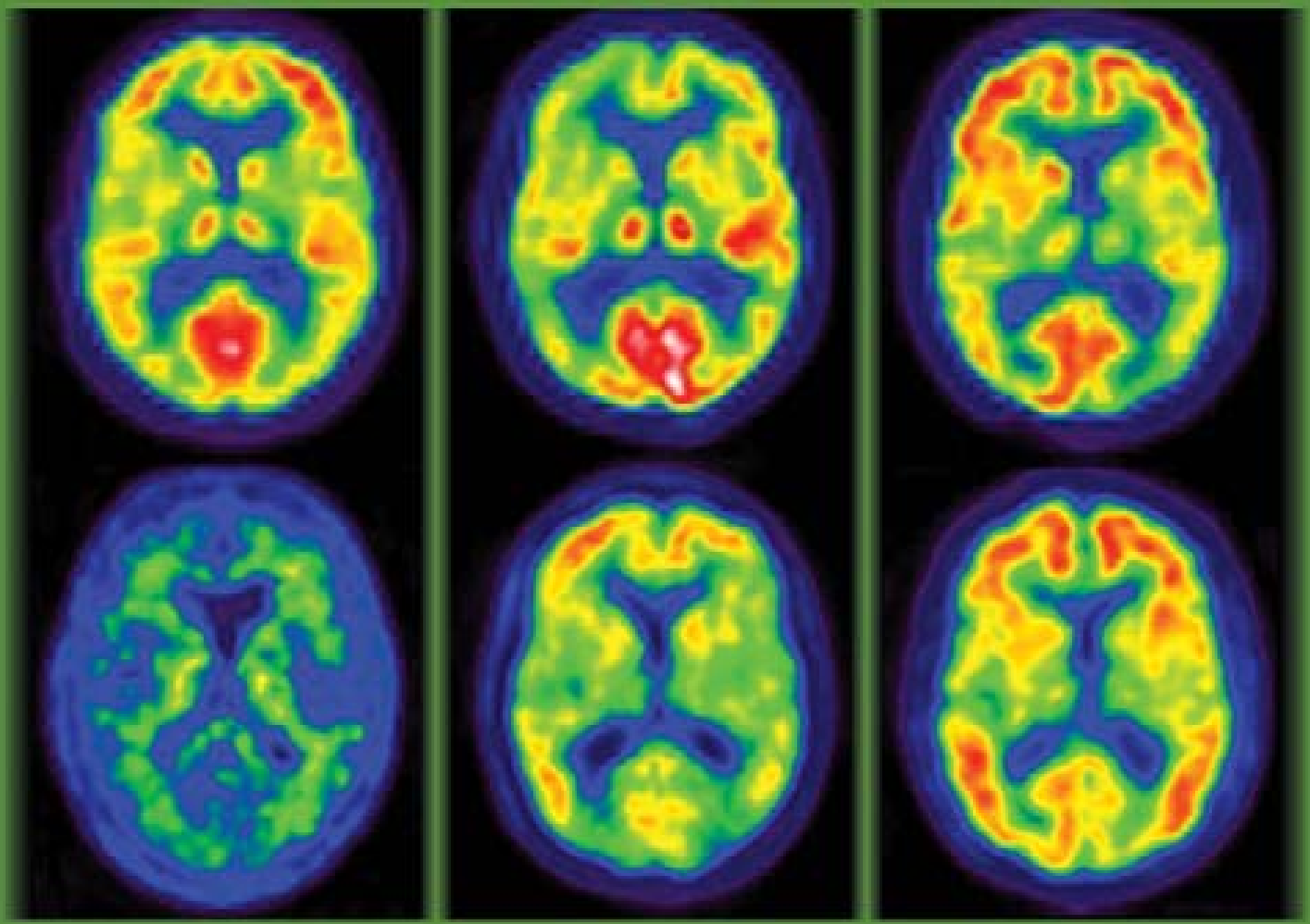
The American Psychiatric Publishing

Textbook of

Alzheimer Disease and Other Dementias



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The American Psychiatric Publishing Textbook of Alzheimer Disease and Other Dementias

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The American Psychiatric Publishing Textbook of Alzheimer Disease and Other Dementias

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Foreword

In a world of ever-growing cognitive complexity, the threat of Alzheimer disease and other cognitive impairments that seem an inevitable part of aging is, on one hand, frightening, and on the other, a call to arms. We are faced with an increasing number of persons with dementia around the world, both in absolute numbers and in percentage of the population. This rise is in part due to greater survival of the normally aging world population and persons with chronic illnesses, head injuries, and other factors affecting brain function. As you will read in the opening chapter, our awareness of dementia has a long history with wide and varied attribution from immorality to evil. From these primitive beginnings, the community of clinicians and scientists has moved to an age of reasoning and inquiry that has created a nosology and diagnostic criteria, developed a knowledge of accompanying pathology, designed trials to test treatments, evaluated psychosocial interventions, provided support to caregivers, and championed the work to preserve the quality of life of those who are afflicted. There has been a virtual explosion of knowledge concerning the dementias in the past 30 years, and scarcely a day goes by that the media fail to mention the possibility of a new treatment for Alzheimer disease.

Psychiatrists seeing persons with dementia in outpatient, inpatient, and long-term care settings have need for a single reference that places the dementia syndromes in the perspective of world health and provides information ranging from day-to-day management to the pathophysiology of the multiple causes of the dementia syndrome. This edition, brought together by the able work of Myron F. Weiner, is a tribute to his long career in clinical care and research in everything Alzheimer. Dr. Weiner has made significant contributions to the treatment of Alzheimer disease, management of behavioral symptoms, and understanding the psychological consequences of dementia and its impact on caregiving. Further, he has worked to identify antecedents of the dementing illnesses such as the impact of cardiovascular risk factors in the development of Alzheimer disease, and he has contributed to raising the awareness of the disease in underserved populations. This sensibility is apparent as one reads through this volume for which he and co-editor Anne Lipton have assembled a group of contributors who are themselves practitioners and clinical researchers dealing with dementia patients each day. They represent international efforts and knowledge with expertise in the complex ethical issues of dealing with dementia, a global awareness of diagnosis, and treatment and management of the disease. The content of this volume reflects a most comprehensive review of cognitive, functional, behavioral, and social aspects of the disease and addresses the interaction between psychopharmacological and behavioral/environmental approaches to disease management.

In the pages that follow, the reader will find important details about state-of-the-art diagnostic methods, including the importance of the probing clinical interview, the value of the medical evaluation, the utility of neuropsychological testing, and the use of current imaging techniques. The current knowledge in these areas allows us to diagnose subtle syndromes such as mild cognitive impairment, and while this entity has significant heterogeneity, there is irrefutable evidence from prospective trials that careful characterization can foreshadow a diagnosis of Alzheimer disease. It is truly a revolutionary idea that we have the potential to predict this progression. The reader will also find that the breadth of cognitive impairment can be quantified allowing for the characterization of a vascular cognitive impairment, sometimes subtle and diffuse, but with significant public health consequences. The hope for newer imaging technologies is described with the goal of having the ability to diagnose earlier, discriminate among disease entities, track subtle change, and provide markers of treatment effect.

As the field of dementia research has progressed, our understanding of different entities has grown, initially focusing on clinical and neuropathological distinctions of frontotemporal dementias and conditions associated with Lewy bodies. Each of these dementias has come under considerable study with many efforts to establish and revise consensus criteria as new information has come forward. These global efforts ensure a common language to

describe serious conditions and lay the foundation to systematically study treatments and management for each.

In fact, starting with the earliest efforts to create research criteria for Alzheimer disease, the field has made remarkable strides in developing treatments. It should be recalled that less than 20 years ago there were no approved treatments, and while the search for more effective treatments and cures goes forward, the Alzheimer patient of today can expect to be offered one of several drugs approved for the treatment of their disease. Approval for the treatment of other dementias has been made possible by the establishment and recognition of diagnostic criteria and development of sound clinical trial design.

The significant behavioral and psychiatric disturbances of dementia are now well acknowledged, leading to important research efforts in treating and managing these manifestations. The chapters of this volume offer the most comprehensive and current view of treatment options and describe both pharmacological and nonpharmacological interventions. As the reader will find, the challenge of addressing these aspects of dementia is great, as is their social and economic impact. Further, the molecular pathology of these syndromes has been elucidated, allowing us to speak of such entities as amyloidopathies, tauopathies, and synucleinopathies and create new ways to understand and potentially attack these diseases.

The dissection of the molecular pathways to the accumulation of amyloid, tau, and synuclein is one of the most exciting advances in dementia research because it provides targets for future interventions. Though it is not yet yielding cures, this line of research has reached the level of clinical trials with both positive and negative results guiding the next step.

As we develop more effective treatments, the needs of those who are afflicted and those who care for them must be addressed. Chapters on approaches to family support and dealing with the dilemma of losing independence through an ethical and legal framework provide critical information that will serve the clinician well. Rigorous research to fill in the gaps of knowledge about patient choice and decision making is ongoing and will maximize the quality of life for current and future generations of patients.

The contributors to this volume indicate that the ultimate aim from a public health and personal choice perspective is prevention. The final section provides thoughtful discussion of the future of dementia. The complex details of current technologies in biomarkers, molecular biology, and drug development for both cures and prevention are presented in a clear and understandable way, to be approachable for both clinician and scientist. Models of disease prevention, through both lifestyle modification and pharmacology, are discussed and evaluated.

This volume provides tools for caring for those with dementia now and hope for those facing it in the future. It will form an important part of the professional library of the psychiatrist of the future.

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Preface

This book had its beginnings in a series of edited volumes first published by American Psychiatric Publishing, Inc., in 1991, with geriatric psychiatrist Myron Weiner as editor. Second and third editions appeared in 1996 and 2003. Reflecting the expansion of the field, neurologist Anne Lipton was invited to coedit the third edition; she continues in this volume. The senior editor is a clinician in an academic medical center where he has been involved with clinical research and clinical care of cognitively impaired elders for more than 20 years. The coeditor also conducts clinical research and has a private neurology practice devoted exclusively to dementia.

When the co-editors approached American Psychiatric Publishing about the possibility of a fourth edition of our earlier work, they (Dr. Robert E. Hales and Mr. John McDuffie) made us an offer we couldn't refuse: to greatly expand the scope and depth of the book and to look beyond the shores of North America in doing so. We have done exactly that and, with the guidance of our international Editorial Board, believe we have done it well.

This book is intended for clinicians as "one-stop-shopping"; it can be read as a clinical guide or as a sourcebook for technical and basic science developments. The disorders we describe are a group of brain conditions that are most easily recognized in their late stage, when they meet DSM criteria for dementia. It was also for easy recognition that we titled this book "Alzheimer Disease and Other Dementias." We are aware that many of the conditions covered in this volume do not meet criteria for dementia; for example, the syndrome of amnestic mild cognitive impairment meets only the memory criterion for dementia. Other subtypes of mild cognitive impairment do not meet the memory criterion, and disorders primarily affecting the frontal lobes or frontal subcortical circuits also do not meet the memory criterion. Our aim, of course, is recognition and treatment of primary brain diseases and systemic disorders affecting the brain before they reach the stage of dementia. Therefore, in addition to using dementia or dementing illness as a generic term in the text of the book, we have often employed the broader terms cognitive disorder (of which dementia is a DSM-IV-TR subheading), cognitively impaired, or cognitive impairment to cover the greater spectrum of cognitive dysfunction and to include the prodromal stage of dementing illnesses.

For the sake of simplicity, we have adopted the term *neuropsychiatric symptoms* to cover the host of behavioral, emotional, perceptual, and ideational symptoms that contribute to the clinical picture of cognitive disorders.

The appendixes include instruments useful to clinicians in their daily practices for grading cognition, function, and neuropsychiatric symptoms. Therefore, we included instruments that do not require extensive props or intensive training and can be administered in settings such as an office, hospital, or long-term care facility. For this reason, we did not include the Alzheimer's Disease Assessment Scale (which requires a highly trained technician and a number of props) or the Clinical Dementia Rating Scale (which requires substantial training of the clinician), although these instruments are used commonly in clinical Alzheimer disease research. We included two forms used at the UT-Southwestern Alzheimer's Disease Center. One is a dementia questionnaire, the other is a functional questionnaire that gives an impression of overall level of function. We tried to select instruments least susceptible to cultural bias, while recognizing that one cannot exclude educational bias from cognitive testing.

To keep up with contemporary usage, we have removed the possessive form from eponymous diseases; Alzheimer's disease is Alzheimer disease, for example, when the term is used in the text and is not part of a proper noun, name of scale, and so on (as in the paragraph above).

We are in debt to many individuals and organizations. We are grateful for our patients and families, who have contributed greatly to our understanding of dementias and without whom this book would not be possible. We thank American Psychiatric Publishing, Inc. for offering us the opportunity to create a comprehensive work on Alzheimer disease and other diseases and conditions that lead to dementia. In particular, we thank Bob Hales and John McDuffie, who also suggested an international edi-

torial board. Board member Ian McKeith suggested that we include a chapter on epidemiology and helped us recruit Carol Brayne and George Savva in London to put it together. Val Shadrack in Carol Brayne's office helped us get through by e-mail to Harald Hampel (formerly in Munich, now in Dublin) and his coworker Katharina Bürger (still in Munich). Chapter author Ed Zamrini, in Salt Lake City, Utah, suggested adding a chapter on traumatic brain injury and led us to Erin Bigler in Provo, Utah, who contributed the chapter. David Drachman supplied much useful information concerning the history of Alzheimer disease research in the United States, and also reviewed Chapter 1, as did Gerda Fillenbaum, who was kind enough to say she actually enjoyed it. John Breitner added scholarly background to this chapter as well. Joachim Herz of Dallas, Texas, reviewed a portion of Chapter 24. Members of our editorial board reviewed first drafts of many chapters.

We are indebted to the Alzheimer's Association for research support and for providing information, support, and advocacy for our patients and their families and to the National Institute on Aging for having funded and guided the University of Texas Southwestern Medical Center's Alzheimer's Disease Center (ADC) and its satellite clinics since 1988.

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Jeanette Weiner and Lee Lipton continue to be patient and understanding, and this book is dedicated to them.

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PART I

Introduction to the Dementias

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CHAPTER 1

Dementia and Alzheimer Disease

Ancient Greek Medicine to Modern Molecular Biology

Myron F. Weiner, M.D.

The topic of dementia received little attention in the medical literature until about 70 years ago. The U.S. National Library of Medicine's PubMed Web site (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) listed only 3 references to dementia in 1935, a total of 25 in 1950, and approximately 550 in 1960. By 2007, there were over 90,000 references. Within the past 30 years, the general public has become familiar with dementia, in large measure due to the efforts of the Alzheimer's Association. People's interest in the topic is evidenced by the fact that the Internet bookseller Amazon.com lists more than 25,000 titles that include the word *dementia*.

With regard to a specific disease, the prevalence of Alzheimer disease in the United States (estimated from a population-based, biracial urban study converted to prevalence estimates and applied to the U.S. population) was 4.5 million in 2000 by one widely accepted estimate (Hebert el al. 2003). This prevalence is expected to nearly triple, to 13.3 million, by 2050. If Alzheimer disease accounts for 56% of dementia cases, as indicated in the Framingham Study (Bachman et al. 1992), the total number of elderly persons in the United States with dementia in 2000 was more than 8 million. A 15-year epidemiological study that initially enrolled more than 1,600 nondemented persons age 65 years or older found that 5% of the deaths were attributed to Alzheimer disease, with an average time from onset to death of 5.9 years (Ganguli et al. 2005). Thus, Alzheimer disease and dementing illness in general are important public health issues, as discussed in Chapter 2 of this volume, "Epidemiology and Impact of Dementia."

History of Dementia

The syndrome now known as *dementia* is a phenomenological diagnosis that is based on clinical observation. It has had various names over the past 2,500 years, including *paranoia*, *idiotism*, *fatuity*, *acquired imbecility*, *senility*, *senile psychosis*, and *chronic organic brain syndrome*. Hippocrates (circa 400 B.C.) identified the brain as the locus of mental function and was the first to recognize disorders of

mental function as diseases, which he divided into epilepsy, mania, melancholia, and paranoia, the last term being equivalent to mental deterioration (Zilboorg 1941).

Although the early symptoms of the syndrome we now call dementia are cognitive and behavioral, astute observers differentiated this syndrome from other mental syndromes on the basis that its early effects were on memory and reasoning, recovery was infrequent, effects on the motor system were late, and it often progressed to total loss of self-care and communication. Causality was of course an issue. It had been observed since antiquity that cognitive functioning might become impaired following head injury or in association with systemic disease, but that in some individuals no association (and therefore no presumed cause) could be found other than with the general deterioration of aging. It had also been observed that persons who lived to old age became increasingly impaired; eyesight and hearing faded, muscle mass and strength diminished, digestion and elimination slowed. These observations gave rise to the concept of *senility*, the gradual wearing out of the organism. There is little doubt that individual organs and tissues do wear out over time; in fact, Drachman (2006a) recently presented an elegant argument for the role of entropy in late-onset Alzheimer disease. On the other hand, too ready an application of the wear-and-tear notion has concealed many of what we call diseases today. The attitude for which Robert Butler (1969) coined the term *ageism* had for many years discouraged inquiry into what appeared to be the "natural" process of physical and mental deterioration and the equation of old age to ill health.

The term *dementia*, which we now use to describe acquired global cognitive impairment (as opposed to *amentia*, or cognitive impairment evident from birth), is derived from the Latin *de* (out of) + *mens* (mind) + *ia* (state of); it literally means a state of being out of or deprived of one's mind. It is one form of *lunacy* or *insanity*; the latter term was still in medical use through the 1920s as the overarching term for severe mental disorders.

The historical origin of the term *dementia* is unclear. Although attributed by Lipowski (1980) to Celsus in the first century A.D., the term does not appear in an English translation of Celsus's (1756) *De Medicina*. The poet Juvenal, in the first or second century, is said to have used *dementia* in reference to the mental decrepitude of old age (Lipowski 1980), but the term was used through the nineteenth century (Thomas 1889) and is still used among the lay public today to designate mental derangements of many kinds. For example, someone might report, "The demented killer stalked his victims with great care and forethought before committing the horrible crime." If the killer had been truly demented, this could hardly have been the case.

The first reference to an association between aging and dementia (i.e., *senile dementia*) was made by Aretaeus of Cappadocia in the second century. In describing the aging process, he used the term *dotage* to mean "a torpor of the senses and a stupefaction of the gnostic and intellectual faculties" that accompanies old age (Aretaeus 1861, p. 301). From at least this point in time, the distinction between normal brain aging and late-life brain disease has been unclear. For example, according to Folsom (1886),

> Senile dementia is simply an excess of the natural weakness of old age out of proportion to the bodily state, an exaggerated childishness of senility to the extent of producing irresponsibility… Memory fails first, and a condition of general weakness of mind follows rapidly afterward. Secretiveness, suspicions, delusions and hallucinations of the special senses are almost always present. (p. 174)

He went on to say (presaging recognition of the frontotemporal dementias and their differentiation from Alzheimer disease),

> It is not uncommon for the early symptoms to consist in an inhibition of the higher faculties of the mind, so that the lower impulses become prominent. The sense of right and wrong and the moral perceptions may become entirely weakened. Acts of indecency, dishonesty, injustice and depravity may follow impaired judgment, and yet so far precede strikingly perverted memory and general intelligence as to make the insanity (e.g., mental disorder) which is obvious to an experienced observer, fail entirely to impress itself on the minds of the community. (Folsom 1886, p. 174)

Philippe Pinel, who in the late 18th century became superintendent of the Parisian psychiatric hospitals named the Bicêtre and the Salpetrière (saltpeter factory), used the term *demence* (i.e., dementia) to designate one of the five classes of mental derangement. Although it is described as the derangement that abolishes the thinking faculty, *dementia* appeared to refer to schizophrenia and other psychotic disorders formerly classified as functional psychoses (Pinel 1806/1962, p. 165). Pinel's class of derangement that most closely corresponds to the DSM-IV-TR (American Psychiatric Association 2000) category of dementia was "idiotism, an obliteration of the intellectual facilities and affections" (Pinel 1806/1962, p. 165). Esquirol (1845/1965), Pinel's successor at the Salpetrière, used *dementia* to describe mental disorders that were manifested by weakened sensibility, understanding, and will, with impaired recent memory, attention, reasoning, and abstracting ability. He described the dementias as acute, chronic, and senile, and included end-stage psychotic disorders and stuporous depression in this category. American physician Benjamin Rush (1812) used the term *fatuity* to designate the mental

disorder characterized primarily by impaired reasoning and memory. James Prichard (1837), an English physician who did not regard dementia as a normal consequence of old age, suggested that dementia might be primary or secondary to other disorders and delineated a four-stage natural history of dementia that parallels the course of Alzheimer disease: 1) loss of recent memory with preservation of remote memory, 2) loss of reason, 3) loss of comprehension, and 4) loss of ability to care for vegetative functions.

Dementia has long had important legal implications as a type of insanity; *insanity* is now exclusively a legal term for a condition in which, as a result of a profound disturbance in the intellectual facilities, a person has lost more or less completely his or her free will and has ceased thereby to be responsible to society for his or her actions. As a result of their diminished capacity to make judgments and direct their own behavior, demented persons were classed under English law as *non compos mentis* or lunatics (Prichard 1837, p. 254) and were held to have diminished responsibility/capacity in relation to the severity of their mental impairment. For this reason, the term *insanity* still persists in legal proceedings, but it was clear to many from the latter part of the 19th century that insanity was in fact the result of a brain disorder (Folsom 1886, p. 104). The first attempts to quantify dementia severity arose because of the need to quantify legal capacity.

Perhaps the earliest schema for quantifying dementia was developed by Hoffbauer (cited by Prichard 1837, pp. 256–261). It included the categories of *bloedsinn* (translated from the German by Prichard as "silliness") and *dumbest* (translated as "stupidity"), which are roughly equivalent to executive deficit and intellectual deficit, respectively. The primary characteristic of silliness was impaired judgment, again anticipating the recognition of frontal lobe syndromes. The primary characteristic of stupidity was inability to acquire and retain information. Stages of silliness, from most to least impaired, included 1) inability to judge new situations, 2) inability to judge familiar situations, 3) marked impairment of memory and attention, 4) clouding of consciousness, and 5) stupor and unresponsiveness. The three stages of stupidity began with the inability to weigh opposites, progressed through the inability to reason, and culminated in the inability to express ideas in language.

Emil Kraepelin (1913) distinguished the so-called functional psychoses from the consequences of obvious brain damage, calling the former the *insanities* and the latter *varieties of imbecility*. The two categories of imbecility were acquired imbecility (dementia) and congenital (ordinary) imbecility. The dementia category included apoplectic dementia due to vascular disease, old age (or senility), and epilepsy.

Eugen Bleuler (1924), in a discussion of the organic psychoses, defined an *organic psychosyndrome* as a set of behavioral manifestations of chronic, diffuse damage to the cerebral cortex that could be due to a variety of causes, including trauma, infection (specifically, syphilis), toxins, arteriosclerosis, and senility. Its manifestations were impairments in memory, judgment, perceptual discrimination, orientation, emotional stability, and impulse control. Bleuler recognized that all cognitive functions were not equally affected, that long-practiced abilities were the most resistant to deterioration, and that some causes of the organic psychosyndrome were still to be discovered. He also noted that variations in the form of the psychosyndrome could be related to genetic factors such as a tendency toward complicating mood disorder in demented persons with a family history of mood disorder. Finally, he pointed out that the course of the organic psychosyndrome was related to the underlying illness, that, for example, the Korsakoff syndrome might improve slightly and remain stable, and that episodes of apparent remission might occur in neurosyphilis and arteriosclerotic brain disease.

Bleuler's textbook contains descriptions of the senile and presenile insanities. Classed under *dementia senilis* are arteriosclerotic insanity and simple atrophy of the brain. Simple *dementia senilis* is described as a product of "the normal regression of the brain that begins in the 50s, but is not usually notable until the last decade of the normal life span" (Bleuler 1924, p. 286) (the actual length of the normal life span is not indicated). The brain shrinks, the ventricles enlarge, and there is disappearance of ganglion (pyramidal) cells. The clinical signs, in order of appearance, are 1) inability to assimilate the ideas of others, 2) increased egocentricity and stubbornness, and 3) confabulation. Bleuler (1924) also set forth the category of *presbyophrenia* (a term he attributed to Kahlbaum), a dementing disorder of old age characterized by constant motor activity, with pacing and repeated performance of meaningless activities. Here, the pathology was said to be senile plaques surrounded by degenerating fibrils (the neuritic plaques of today), whereas in Alzheimer disease, the pathology was said to be more intense, with rapid development of aphasia, agnosia, and apraxia.

At mid-twentieth century, Roth and Morrissey (1952) wrote that resulting from the work of Alzheimer, Kraepelin, Binswanger, Pick, and others, the mental diseases peculiar to old age had, since the beginning of the century, been subdivided into the senile, arteriosclerotic, and presenile psychoses (*psychosis* in this case meaning a mental disorder of sufficient severity to interfere with meeting the demands of everyday life). They regarded Alzheimer and Pick diseases as rare presenile illnesses. Roth and

Morrissey described the core syndrome of senile psychosis as beginning with selective impairment of recent memory and attention and faulty location of recent events in time, followed by euphoria, confabulation, and an ill-systematized paranoid element deriving from failure of memory. They recognized that this symptom complex could be the clinical manifestation of a number of underlying brain diseases. In the same paper, Roth and Morrissey reported on the 3-year survival of 150 consecutive persons age 60 years or older who had been admitted to Graylingwell Hospital in 1948. Of those with affective diagnoses, less than 25% were dead; however, 90% of those diagnosed with senile psychosis had died. Despite the fact that the modal patient with an affective disorder diagnosis was in the age range 60–65 years and the modal patient with senile psychosis was in the age range 75–79 years, this finding was probably the first statistical proof of the lethality of senile psychosis.

It has long been recognized that there is an indistinct border between what Ferrara (1959) termed *psychological/physiological senescence* (the effects of normal social/brain aging) and *pathological senescence* (dementia). Ferrara stated that as physiological and psychological senescence gradually drifts into pathological senescence, perceptual and memory impairments are often encountered, and that impaired perception, impaired registration, and decreased impressionability often mark the onset of a senile dementia. "From a practical standpoint, one may speak of dementia when the disturbance of memory is such as to render fragmentary or falsify entirely the relationship of the patient to his surroundings" (Ferrara 1959, p. 1025).

As the etiologies of various dementing illnesses have been elucidated and treatments developed, the prevalence and impact of these illnesses have changed. For example, general paralysis of the insane (now termed *neurosyphilis*) was described by Thomas Willis in 1672 as a syndrome beginning with mania and followed by dementia and paralysis, but the paralysis was thought to be a late, nonspecific concomitant of mental disease. In 1826, Bayle recognized the entire cluster of signs and symptoms as a specific entity. The relationship of this syndrome to syphilis was hotly debated until 1913, when the spirochete *Treponema pallidum* was demonstrated in the brains of persons with general paresis by Noguchi and Moore, and the term *neurosyphilis* came into use (Henry 1941). Since the 1940s, with the widespread use of serological tests to detect early syphilis and the availability of penicillin for treatment, neurosyphilis has become relatively rare in the United States. In fact, the rate of first admissions to psychiatric hospitals because of neurosyphilis fell from 4.3/100,000 population in 1946 to 0.4/100,00 in 1960 (Adams and Victor 1989, p. 573).

The prevalence and impact of dementia due to metabolic causes have also changed as a result of medical discoveries. Wilson disease is now treatable, the dementia of AIDS (acquired immunodeficiency syndrome) is largely preventable, and obstructive hydrocephalus due to meningitis can be relieved surgically. Early conjectures about the relationship between alcohol consumption and dementia may have implicated the wrong agent. Despite the association of dementia with repeated episodes of delirium tremens noted in the 19th century (Wilson 1886), Victor et al. (1989) found no evidence for direct toxicity of alcohol at postmortem examination of persons diagnosed during life as having alcoholic dementia. Instead, they demonstrated the stigmata of the thiamin deficiency–related Wernicke syndrome and other unrelated conditions, including trauma and Alzheimer disease. Thus, the primary cause of dementia in alcoholics appears to be malnutrition rather than the direct toxic effect of alcohol on the brain.

Alzheimer Disease: From Clinical Description to a Theory of Disease and Treatment

The story of Alzheimer disease began with a series of clinical observations that were linked to a type of brain pathology. These clinical and pathological observations have led to theories of pathophysiology, which in turn have pointed to possible pathways to treatment. The time from disease recognition to the first symptomatic treatment was nearly 90 years. Treatments aimed at altering the disease process are still in development.

The story began on April 8, 1906, when psychiatrist Alois Alzheimer (Figure 1–1) examined the brain of Auguste D, a woman who at age 51 years had been admitted, on November 25, 1901, to the Hospital for the Mentally Ill and Epileptics in Frankfurt, Germany. Her family physician's admittance note indicated that she had been suffering for a long time from weakness of memory, persecution mania, sleeplessness, and restlessness and that she was no longer able to do any physical or mental work. Alzheimer had seen her at the Frankfurt facility, but in 1903 had joined Emil Kraepelin at the Royal Psychiatric Clinic in Munich, where Alzheimer became head of the Anatomical Laboratory (Figure 1–2) (Goedert and Spillantini 2006).

It was here that Alzheimer received the woman's brain following her death. Grossly, he noted brain shrinkage and

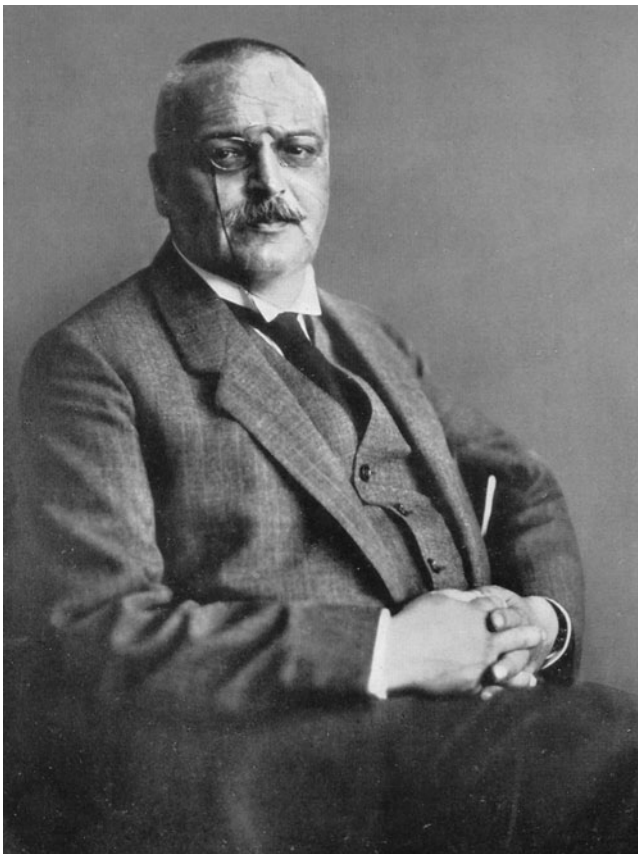

FIGURE 1–1. Alois Alzheimer, M.D.
Source. Department of Psychiatry, Ludwig Maximilian University Munich. Used with permission.

FIGURE 1–2. Alzheimer laboratory in Munich.
Source. Department of Psychiatry, Ludwig Maximilian University Munich. Used with permission.

mild hydrocephalus ex vacuo. On applying the recently developed Bielchowsky silver stain to brain slides, he noted fibrils that stained differently from normal neurofibrils and millet seed–sized lesions containing a peculiar substance distributed throughout the outer layers of the entire cerebral cortex. His findings were published in 1907 (Alzheimer 1907/1987); he thought the disease was a rare form of presenile dementia. By 1908, Alzheimer and his colleague Perusini had found a total of four cases of presenile dementia, all of whom had similar pathology (Maurer 2006). Only 2 years later, Kraepelin (1910) (Figure 1–3) included the eponym Alzheimer's disease in his textbook of psychiatry. Despite the fact that both plaques and tangles had been described earlier by other investigators (Drachman 2006b), the name stuck.

Belying the paucity of references in PubMed cited earlier, there was a lively discussion in the literature of the 1920s and 1930s concerning the clinical signs and symptoms of Alzheimer disease, the relationship of histopathology to clinical symptoms, and the relationship of Alzheimer disease to senile dementia (reviewed in Newton 1948). However, it did not become widely accepted that Alzheimer-type change in brain had a strong relationship to senile-onset dementia until the work of British pathologist J.A.N. Corsellis (1962). Corsellis performed postmortem studies of the brains of institutionalized persons with diagnoses such as schizophrenia, affective disorders, and paranoid disorders and compared them with the brains of persons having diagnoses of senile dementia or mixed senile/vascular dementia, but not with those of persons diagnosed clinically with other brain diseases. He found that 80% of the senile dementia group showed moderate to severe plaque formation. Patients with psychiatric diagnoses had only moderate to severe plaque formation if they lived to be age 75 years or older. Neurofibrillary tangles occurred almost exclusively in persons diagnosed with senile and mixed senile/vascular dementia. These tangles tended to parallel the plaque density, and their frequency was not related to patient age. In the same year, Kay (1962) noted that a diagnosis of senile dementia was associated with markedly reduced life expectancy.

Sim and Sussman (1962) published the course of 21 cases of biopsy-proven and neuropathologically proven Alzheimer disease. They still considered the disease to be a presenile dementia, although Simchowitz, who first used the term *senile plaque* and had also described granulovacuolar degeneration, had written in 1914 that there was no difference between Alzheimer disease and senile dementia (Simchowitz 1914). Sim and Sussman compared the clinical picture of persons seen in years 1–4 of symptoms. They found amnesia and disorientation to be the earliest symptoms, dysphasia as intermediate, and apraxia and manifest dementia to occur later. They noted that in the early stages, despite poor orientation and memory loss, patients were not demented and were able to organize themselves and their environment to a remarkable degree, evidencing what we might now call *mild*

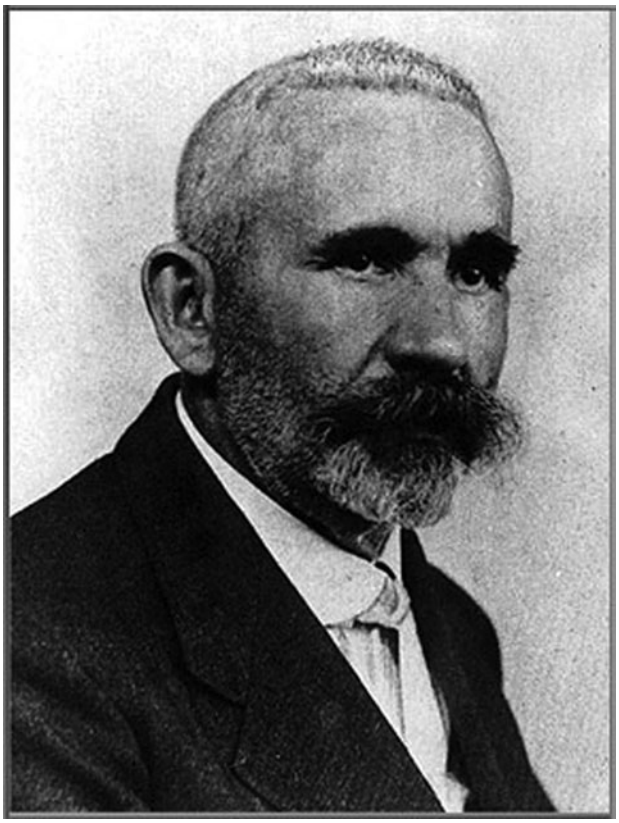

FIGURE 1–3. Emil Kraepelin, M.D., who named Alzheimer disease.
Source. Department of Psychiatry, Ludwig Maximilian University Munich. Used with permission.

cognitive impairment according to the criteria developed by Petersen et al. (1999). The work of Sim and Sussman also set the stage for the later development by Rosen et al. (1984) of the Alzheimer's Disease Assessment Scale, which became one of the two standard assessment instruments in subsequent clinical trials of medication for Alzheimer disease. In 1963, electron microscopy showed that neurofibrillary tangles consisted of paired helical filaments (Kidd 1963). Three years later, Roth et al. (1966) examined the brains of patients ages 60 years and older who had been seen in a psychiatric or general hospital, had been evaluated cognitively, and did not have evidence of stroke. He came to the following three conclusions:

> Far from plaques being irrelevant for the pathology of old-age mental disorder, the density of plaque formation in the brain proves to be highly correlated with quantitative measures of intellectual and personality deterioration in aged subject. The establishment of a valid measure of cerebral damage in one group of organic psychoses opens up the possibility of defining and measuring the psychological defects that show the best correlation with measures of cerebral damage. …As the brain is an organ with a fixed cell population and such organs have long been known to be particularly liable to the changes of senescence, the facts suggest that senile plaque formation and related processes may also deserve investigation with more precise techniques than those in this study, for their possible relevance to the problems of ageing in man. (Roth et al. 1966, p. 110)

Years later, a stronger correlation was shown between cognitive impairment and reduction in synaptic density (DeKosky and Scheff 1990), but it is still not known if the age-related accumulation of amyloid plaques in the brain is a normal product of aging or a precursor of the neuritic plaques of Alzheimer disease (Knopman et al. 2003).

Roth and his group (Tomlinson et al. 1968, 1970) then compared the brains of older adults who displayed no objective evidence of cognitive impairment prior to death with those of persons with well-documented dementia. Statistically significant between-group differences were found in cortical atrophy, ventricular dilatation, senile plaque formation, "Alzheimer's neurofibrillary change," and granulovacuolar degeneration.

Because memory impairment is typically the presenting symptom of Alzheimer disease, researchers attempted to understand and treat this symptom by integrating the biology of memory with the pathophysiology of Alzheimer disease. Deutsch (1971) suggested that the cholinergic system is the biological substrate of memory. Subsequently, David Drachman (Figure 1–4) (Drachman and Leavitt 1974) showed that scopolamine blocked storage in long-term memory with relative sparing of recall and retrieval from long-term memory, a pattern similar to that of normal aging.

Searching for the relationship between neuropathology and brain function, Davies and Maloney (1976) assayed postmortem levels of enzymes associated with the neurotransmitters acetylcholine, γ-aminobutyric acid (GABA), dopamine, noradrenaline, and 5-hydroxytryptamine in 3 subjects with Alzheimer disease and 10 control subjects. Levels of choline acetyltransferase, the enzyme forming acetylcholine, and acetylcholinesterase, which hydrolyzes acetylcholine in the synapse, were dramatically reduced in the Alzheimer brains; the level of reduction coincided with the areas containing the greatest number of neurofibrillary tangles. The following year, White et al. (1977) confirmed that the presynaptic cholinergic marker choline acetyltransferase was reduced in subjects with Alzheimer disease, but also found intact postsynaptic receptor binding, suggesting that treatment with centrally acting cholinesterases might be beneficial before neuronal loss was advanced. The potential utility of this approach was underscored by the finding of massive cell loss in Alzheimer disease in basal forebrain nuclei, including the nucleus basalis of Meynert, a poorly defined

FIGURE 1–4. David A. Drachman, M.D., created a pharmacologic model of age-related cognitive change.
Source. Courtesy of Dr. Drachman. Used with permission.

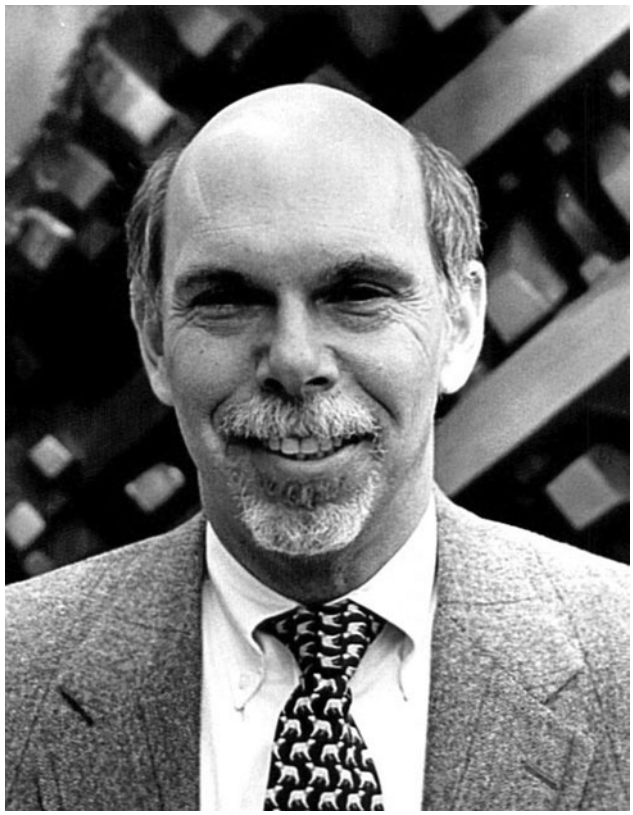

FIGURE 1–5. Kenneth L. Davis, M.D., showed memory-enhancing property of physostigmine.
Source. Courtesy of Dr. Davis. Used with permission.

group of neurons located dorsal to the optic chiasm that supplies most of the cholinergic innervation to the cerebral cortex (Whitehouse et al. 1981).

Experimentation with the anticholinesterase physostigmine by Kenneth Davis (Figure 1–5) led to the observation that it improved memory in cognitively intact individuals (Davis et al. 1978) and persons with Alzheimer disease (Davis and Mohs 1982), but the short half-life of this drug and the need for parenteral administration made it unsuitable for clinical use. At the same time, the long-acting cholinesterase inhibitor tacrine was being investigated clinically, following the clinical observation that it effectively reversed anticholinergic delirium following overdose of tricyclic antidepressants (Summers et al. 1981). Following the publication of a large multicenter study by Davis et al. (1992), the U.S. Food and Drug Administration approved tacrine for the treatment of Alzheimer disease in 1993. Other cholinesterase inhibitors were later approved, and the use of tacrine gradually vanished because of the need for frequent dosing, slow titration, and hepatotoxicity. Overall, these drugs produce small, transient cognitive improvement and modest, if any, effect on disease progression, as would be expected from a symptomatic treatment.

The 1980s saw progress in elucidating the neuropathology and pathophysiology of Alzheimer disease. Glenner and Wong (1984a) sequenced from blood vessel deposits of patients with Alzheimer disease the substance that had been recognized in the core of neuritic plaques as amyloid protein (Terry et al. 1964). Based on work published the previous year showing the presence of Alzheimer disease pathology to be ubiquitous in persons with Down syndrome who had reached age 40 years, Glenner and Wong (1984b) showed that the amyloid in Down syndrome was identical to that found in patients with Alzheimer disease. Korenberg et al. (1989) later showed that the portion of chromosome that is reduplicated in trisomy 21 Down syndrome contains the amyloid precursor protein, suggesting that the cause of Alzheimer disease in these persons is overloading of the proteolytic pathway of normal amyloid precursor protein. The subsequent work in molecular genetics began with the localization of a gene for familial Alzheimer disease to chromosome 21 (St. George-Hyslop et al. 1987). It will be reviewed in Chapters 8, "Alzheimer Disease," and 24, "The Molecular and Ge-

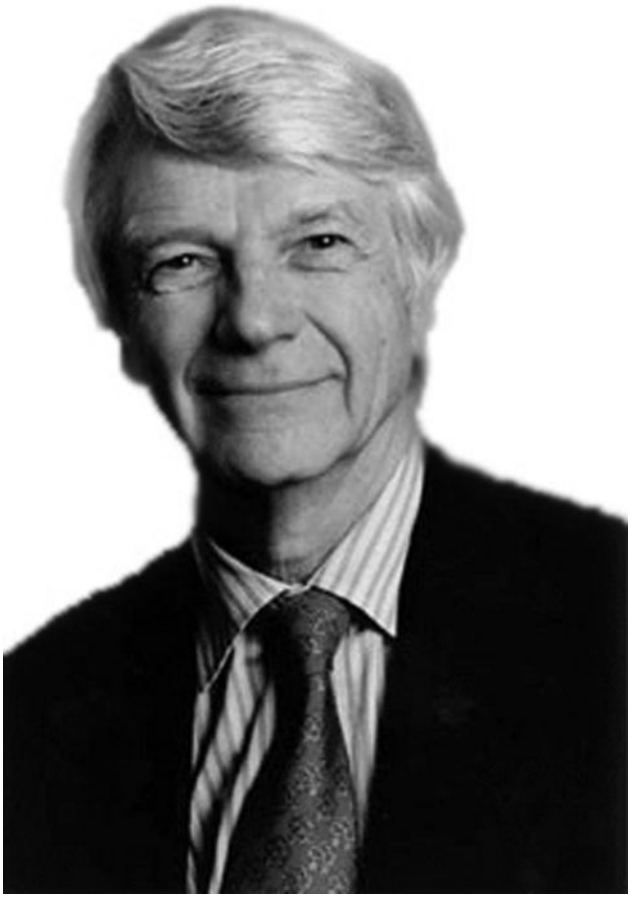

FIGURE 1–6. Robert N. Butler, M.D., first head of the National Institute on Aging.
Source. Courtesy of the International Longevity Center. Used with permission.

FIGURE 1–7. Zaven Khachaturian, M.D., first associate director of the Neuroscience and Neuropsychology of Aging Program of the National Institute on Aging.
Source. Courtesy of Dr. Khachaturian. Used with permission.

netic Basis of Alzheimer Disease," as will the amyloid cascade hypothesis of Alzheimer disease, the possible neurotoxicity of amyloid beta oligomers (Walsh and Selkoe 2007), and the major risk factor for late-onset Alzheimer disease—the inheritance of the ε4 allele of the cholesterol-transporting protein apolipoprotein E (Corder et al. 1993)—and its possible relationship to the formation of neurofibrillary tangles.

Robert Katzman's (1976) editorial in the *Archives of Neurology* pointing out the prevalence of Alzheimer disease and its impact on life span is widely credited for sparking Alzheimer disease research in the United States (Khachaturian 2006). Congress had authorized creation of the National Institute on Aging (NIA) in 1974. By 1976, the institute was formally organized under the direction of psychiatrist Robert Butler (Figure 1–6), and in 1978, it began its program of extramural research on brain aging and Alzheimer disease under the leadership of Zaven Khachaturian (Figure 1–7). In 1979, the Alzheimer's Association (first named the Alzheimer's Disease and Related Disorders Association; ADRDA) was formed with encouragement and support from the NIA and the National Institute of Neurological and Communication Disorders and Stroke (NINCDS); Mr. Jerome Stone became President, and Drs. Robert Katzman and Carl Eisdorfer cochaired the Medical Advisory Board (Alzheimer's Association 2008).

The year 1981 saw the publication of a government-industry–academia collaboration titled *Strategies for the Development of an Effective Treatment for Senile Dementia* (Crook and Gershon 1981) that stimulated some of the early U.S. drug trials. The title of the follow-up volume, *Treatment Development Strategies for Alzheimer's Disease* (Crook et al. 1986), indicated the recognition that senile dementia and Alzheimer disease were the same pathological entity. Between these two publications, on the advice of the NINCDS National Advisory Council, NINCDS and ADRDA formed the Work Group on the Diagnosis of Alzheimer's Disease to establish clinical diagnostic criteria so that the natural history of the disease could be better characterized and meaningful clinical

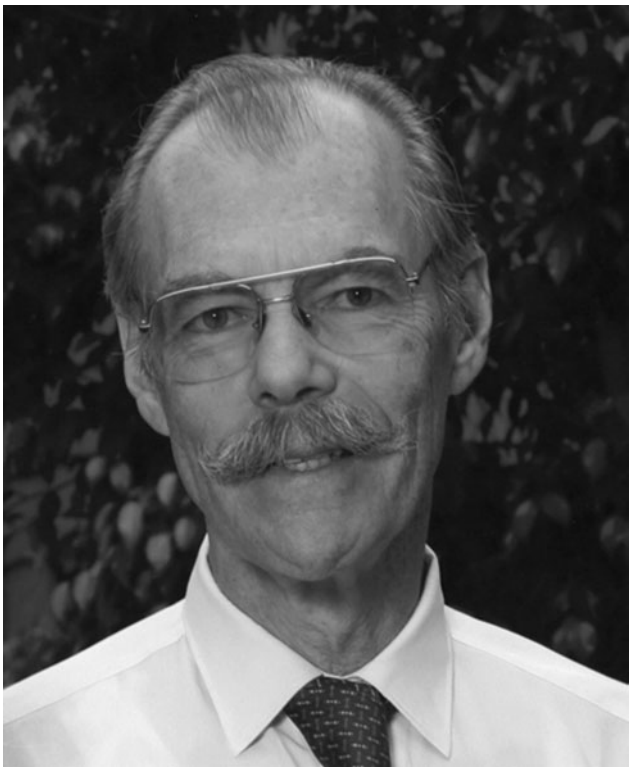

FIGURE 1–8. Leon J. Thal, M.D., first head of the Alzheimer's Cooperative Study.
Source. Courtesy of the Department of Neurosciences, University of California at San Diego. Used with permission.

trials undertaken. The diagnostic criteria that were formulated for possible and probable Alzheimer disease (McKhann et al. 1984) continue in use as the basis for enrollment in clinical trials. Morris and Rubin (1991) reported that these criteria have 80%–90% accuracy. A recent review of autopsy cases (Ranginwala et al. 2007) finds this accuracy rate essentially unchanged despite advances in immunohistochemistry that now enable more ready detection of Lewy bodies and tauopathies other than the neurofibrillary tangles of Alzheimer disease.

In 1986, a grant from NIA enabled the creation of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) to standardize the clinical, neuropsychological, and neuropathological evaluation of persons with suspected Alzheimer disease. In this effort, led by Dr. Albert Heyman of Duke University, patients with Alzheimer disease and control subjects without dementia were recruited from 24 NIA-sponsored Alzheimer's disease centers and from other university programs in the United States. Subjects were examined at entry and annually thereafter, to observe the natural progression of Alzheimer disease. Autopsy examination of the brain was included, to the extent possible. The major standardized instruments developed by CERAD are now used by many Alzheimer disease research centers in the United States and abroad, by physicians in clinical practice, and in population-based surveys. Data were obtained on more than 1,000 nationally distributed white and black patients with Alzheimer disease and nearly 500 control subjects without dementia. In this series, the clinical diagnosis of Alzheimer disease based on NINCDS-ADRDA criteria was confirmed in 87% of autopsied cases. The CERAD database is still available to investigators (http://cerad.mc.duke.edu).

In 1991, the Alzheimer's Disease Cooperative Study was funded by NIA under the direction of the late Leon Thal (Figure 1–8) to provide an infrastructure for clinical trials of substances that have included estrogen and nonsteroidal anti-inflammatory agents.

Most recently (2004), the Alzheimer's Disease Neuroimaging Initiative was established with resources from the National Institute on Aging, the National Institute for Biomedical Imaging and Bioengineering, the Foundation for the National Institutes of Health, the Alzheimer's Drug Discovery Foundation, and the Alzheimer's Association to examine how brain imaging technology can be used with other biological marker tests to measure the progression of mild cognitive impairment and early Alzheimer disease. This information will then be used to aid future clinical trials by providing a standard assessment tool to measure treatment effects (Mueller et al. 2005).

Dementia and Society

Dementia is, and always has been, a substantial social issue. Because it is a cluster of cognitive and behavioral symptoms, the dementia syndrome was technically a mental disorder and was long the purview of the institutionally based alienist, the forerunner of today's psychiatrist. Before the recognition of mental disorders as a form of illness in the fifteenth and sixteenth centuries, persons with dementia lived in almshouses or wandered the streets when they could no longer be contained by their families. Between the late eighteenth century and the late nineteenth century, individuals with mental illness made a gradual transition to psychiatric hospitals. Psychiatric hospitals (the first was built in Valencia, Spain, in 1409) (Mora 1980) were originally asylums, places of refuge for persons with diseases of the mind in which the treatments of the day could be administered while the residents were sheltered from the public at large and vice versa. In the United States, these institutions were administered by state governments using state funds. By the middle of the twentieth century, the proportion of elders in these insti-

tutions had increased because of the aging of Americans; in the year ending June 30, 1945, senile or arteriosclerotic psychoses were the diagnoses of 42% of first admissions to the Worcester State Hospital in Massachusetts (Katzman and Bick 2000). For many years, a substantial portion of individuals housed in these state-run psychiatric facilities were persons with dementia who had been admitted initially for behavioral disturbance but for whom these facilities primarily provided food and shelter, often because there was no family to which these persons could be returned.

Beginning in the 1950s, the use of psychotropic drugs for reducing behavioral disturbance, the increasing concern for civil rights, and the federal stipulation that Medicaid funds may not be used for the care of patients in freestanding state psychiatric facilities all reduced the use of state psychiatric hospitals as asylums, with the result that dependent patients with dementia are now more frequently housed in other types of long-term-care facilities such as boarding homes and nursing facilities. Although it is possible to involuntarily confine persons with dementia to psychiatric hospitals by means of court commitment, there is no legal means to restrain these individuals to other facilities, and those who insist on their independence often reside on the streets or in jails, the latter as a result of their impulsivity and poor judgment. Those dementia patients who can accept care by their families will pose an increasing burden to their families as our population continues to age.

Dementia and DSM

Attempts made in the United States to develop a standardized nomenclature of diseases began in 1927 and culminated in the publication of the *Standard Classified Nomenclature of Disease* in 1933 (Logie 1933). Long before that, in 1917, the Committee on Statistics of the American Medico-Psychological Association (forerunner of the American Psychiatric Association) had formulated a plan for the uniform collection of disease-related statistics in psychiatric hospitals. For a number of years, *The Statistical Manual for the Use of Hospitals for Mental Disease* was published by the National Association for Mental Health, but it became clear to the Armed Forces and the Veterans Administration during and after World War II that a nomenclature based largely on diseases treated in psychiatric hospitals was not adequate to cover the spectrum of psychiatric disorders.

In 1948, the Committee on Nomenclature and Statistics of the American Psychiatric Association undertook amalgamating the various existing nomenclatures; those efforts culminated in the publication of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I; American Psychiatric Association 1952). In DSM-I, mental disorders were divided into two major groups: 1) those in which disturbance of mental function resulted from impaired brain function and 2) those in which altered brain function resulted from a more general difficulty in adaptation. The disorders caused by or associated with impairment of brain tissue function included two categories: acute (reversible) brain disorders and chronic (irreversible or only partially reversible) brain disorders. Both of these categories were subdivided according to the underlying disease or condition, the latter including Alzheimer disease, at the time considered as a disease of presenile onset, and chronic brain syndrome, which was associated with senile brain disease. The 1948 edition of *The Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death* (World Health Organization 1948) had included the categories of presenile psychosis (which excluded so-called presenile brain diseases such as Alzheimer and Pick disease), senile psychosis, and psychosis with cerebral arteriosclerosis.

The nomenclature of DSM-II (American Psychiatric Association 1968) was coordinated with the 1967 publication of the *International Classification of Diseases, 8th Revision* (ICD-8; World Health Organization 1967). In DSM-II, organic brain syndromes were listed in two categories: psychoses associated with organic brain syndromes and nonpsychotic organic brain syndromes. The term *psychosis* was used to indicate that the condition described "sufficiently impaired mental functioning to interfere grossly with the capacity to meet the ordinary demands of life" (p. 23). The term *dementia*, which did not appear in DSM-I, appeared in the categories of senile dementia and presenile dementia. *Acute* and *chronic* became modifying terms.

DSM-III (American Psychiatric Association 1980) stated that differentiation of organic mental disorders as a separate class did not imply that nonorganic (e.g., functional) mental disorders are independent of brain processes. Under the category of organic mental disorders was the subcategory of organic brain syndromes, a group of phenomenological diagnoses unrelated to underlying disease. These syndromes were grouped into six categories, one of which was delirium and dementia, in which cognitive impairment is relatively global. Other categories included amnestic syndrome and organic hallucinosis, organic delusional syndrome and organic affective syndrome, organic personality syndrome, intoxication and withdrawal, and atypical or mixed. This section was followed by the individual organic mental disorders, including primary degenerative dementia (Alzheimers disease) and multi-infarct dementia.

DSM-IV (American Psychiatric Association 1994) replaced the category of organic mental disorders with the category of delirium, dementia, and amnestic and other cognitive disorders, because the term *organic mental disorders* implied that the other disorders in the manual did not have an "organic" component. An additional important change in DSM-IV was introduction of the phrase, "due to…" This phrase indicated that the clinician, in addition to describing the psychiatric symptom cluster, needs to attempt an identification of the underlying pathophysiological process. This phrase is also used in DSM-IV-TR (American Psychiatric Association 2000) and brings us back to the notion proposed first by Hippocrates and reaffirmed 2,000 years later by the German physician Wilhelm Griesinger in 1845 that all mental disorders are diseases of the brain (Zilboorg 1941).

There are still many unanswered and perhaps unanswerable questions with regard to the nosology of disease in general and dementia in particular. How far can nominalistic categorization be carried before it becomes trivial or moot? For example, is it of any heuristic value to code dementia of the Alzheimer type as *with early onset* or *with late onset*? The *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10), continues to have a residual category of presenile and senile dementia (World Health Organization 1992). To what end? Is this not the same disease? However, if we did not continue this process and attempt to make increasingly fine distinctions, we probably, for example, would have failed to detect and distinguish those frontotemporal dementias whose basis is abnormal metabolism of the microtubule-associated protein tau from Alzheimer disease, whose pathophysiology appears related to errors in the metabolism of the amyloid precursor protein embedded in every human cell membrane (Boeve 2006). Or is it? Drachman (2006a) suggested that instead of a single metabolic defect underlying all of what is now seen as a single disease, there may be multiple age-dependent factors in late-onset sporadic disease that may be unique to each individual, depending on that person's vulnerability or cognitive reserve. But what about the effects of aging? Cannot the nervous system simply wear out over time? Our job is to sort out the potentially remediable causes of human disability and suffering from the inevitable organ failure and death of human beings. It is a daunting task that begins with astute clinical observation and classification.

Beyond DSM

Krishnan (2007), in a discussion of the concept of disease in geriatric psychiatry, made the case for uniting descriptive syndromal (*nominal*) diagnosis with *essential* diagnosis (i.e., diagnosis of the related and presumably causative biological processes). The designation of certain signs and symptoms as indicators of disease paves the way for rational understanding and rational treatment. However, what is rational depends on the dominant cultural ideology. If deviations from the expected norm of behavioral or physical function are related to whims of the gods or to transgressions against them, rational treatment is placation of the proper deity or deities. If the deviations are due to an imbalance of bodily fluids or humors, attempts to rebalance by bleeding or purging make sense. What is rational in the age of molecular biology? Should not diseases be seen in essentialist terms as disturbances at a molecular level and labeled accordingly? Should not the offending underlying process be elucidated and repaired by genetic manipulation or by altering the structure, function, or interaction of the proteins encoded by those genes? Would it not be more reasonable to speak of Alzheimer disease in one person as a cerebral amyloidopathy associated with homozygosity for the ε4 allele of apolipoprotein E, and in another as a cerebral amyloidopathy associated with an overload of amyloid precursor protein processing due to reduplication of the 21q22 band of chromosome 21?

Specificity is gained in this process of essentialistic molecularization, but something is also lost, and that is the clinical picture of the disease that leads to its diagnosis and a confounding of associated molecular mechanisms with etiology. Thus far, the ε4 allele and Alzheimer disease are only associated; a causal chain has not been established. In the case of Down syndrome, the link is still largely associative; not all persons with 21q22 reduplication develop clinical Alzheimer disease. These molecular diagnoses do not explain why *that* person began to manifest *this* disease in this way at this particular point in time. It is likely that the closest we can come to resolving the behavioral-molecular polarity is to make them stand together, as has already been done with the phrase "due to" following the psychiatric syndromal diagnosis in DSM-IV-TR. The "due to" portion of the diagnosis has the potential for further elucidating etiology, but we must be careful that it does not also further cloud our vision.

Beyond Dementia

At present, with the exception of genetic testing of persons who are by history at risk for early-onset familial Alzheimer disease, Huntington disease, or certain other hereditary metabolic disorders, we are largely unable to predict which asymptomatic persons will eventually develop dementing illnesses. Delaying the diagnosis of de-

menting illness until individuals show signs of dementia improves diagnostic accuracy but reduces the chance of introducing treatment early enough that individuals can still be effective family members or productive members of society. The aim must be to detect markers that identify potentially dementing illnesses before they cause significant impairment. This is the reason that the concept of mild cognitive impairment was developed by Petersen et al. (1999), and this is the goal of the federally funded Alzheimer's Disease Neuroimaging Initiative (Mueller et al. 2005).

KEY POINTS

- Clinical observation is the starting point of medical science. We must not assume that all possible diagnostic entities have already been described and that the job of the clinician is to place the patient's signs and symptoms in the appropriate pigeonhole. In Alzheimer's (1907/1987, p. 8) words, "It behooves us not to be satisfied with attempts, by means of painstaking efforts, to make clinically unclear observations to fit one of the disease categories familiar to us."
- Association is not causation.
- Theories are helpful organizing principles, but clinical observation must be atheoretical.
- Theory follows observation, although theory may at times sharpen observation and lead to more definitive conclusions. Without the theory of infectious agents, it would not have been possible to ascertain the cause of general paralysis of the insane.
- All diagnostic schemas are starting points for clinical observation and are useful only so long as they do not block further exploration. Because motor symptoms followed mental symptoms in general paresis, first classified as a mental illness, it was assumed that they were nonspecific by-products of mental illness and not indicative of a specific illness.
- Dementia is the end product of diseases that we are trying to identify early enough to prevent them from manifesting as dementia.

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CHAPTER 2

Epidemiology and Impact of Dementia

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In Chapter 1, "Dementia and Alzheimer Disease: Ancient Greek Medicine to Modern Molecular Biology," Weiner described the development of the understanding of dementia. In this chapter, we focus on what is known about the distribution of dementia in the population and describe the social and economic consequences of dementia. As with most disorders, there are many factors that affect the occurrence and recognition of dementia in an individual and therefore the pattern of its prevalence in a population. Age is the most apparent and consistent of these factors in that the risk of dementia incidence doubles every 5 years after the age of 55. Dementia is also linked with specific genetic markers, comorbid health conditions, and factors related to sociodemographics, culture, and lifestyle. Understanding these associations should lead to improvements in primary prevention, better understanding of the etiology, and earlier identification of dementia. Meanwhile, the development of social and clinical interventions offers the prospect of reducing the impact of dementia on the lives of people it affects and the wider economy.

Dementia as a Clinical Entity

The study of dementia depends on its precise definition and its assessment, which have varied through time and still vary across communities. Dementia is a clinical syndrome; it is defined by a set of clinical criteria that must be fulfilled for a diagnosis to be made. There are several commonly used formal definitions, each of which requires cognitive decline and memory loss that is severe enough to interfere with an individual's social or occupational functioning. In this book, the diagnosis of dementia is examined in depth in Part II, "Evaluation and Diagnosis of Dementia." Dementia in an individual is caused by one or more of many underlying pathologies, as indicated in Chapter 1. The most common of these are Alzheimer disease and vascular disease in the brain. Part III of this book, "Alzheimer Disease and Other Dementias," examines in detail the different disorders that cause dementia, including their clinical course, specific physical and neurological consequences, and treatments.

Although much work has been done toward understanding degenerative neuropathologies, their exact role in causing dementia is not well understood. Considerable overlap exists in the symptoms caused by the most common dementing disorders, and it is often difficult to determine the specific cause of dementia in an individual, particularly in the oldest-old patients. Furthermore, neuropathological findings in the older population commonly reveal more than one disorder in a large proportion of dementia cases (Medical Research Council Cognitive Function and Ageing Study 2001; Schneider et al. 2007). For these reasons, discussions of epidemiology and of social and economic impact usually focus on dementia as a disorder.

Epidemiology

Understanding a disorder's epidemiology—that is, the pattern of its occurrence in the population—is essential for effective population-based research and health management. Good estimates for the prevalence of dementia and its distribution in the population are needed for planning social and health care services and for measuring its impact on a population. Routine health contact information and mortality statistics have repeatedly been shown to seriously underestimate dementia in the population (Macera et al. 1992); therefore, population-based studies are needed to measure its prevalence.

The incidence of dementia is the rate at which new cases occur and is usually quoted in terms of the risk per person per year. Dementia incidence is estimated using prospective studies in which a cohort undergoes repeated assessments, with new cases identified at each assessment.

Prevalence is increased by an increase in incidence or an increase in average duration of illness. Because most conditions that produce the clinical syndrome of dementia are not reversible, duration of illness is equivalent to survival time. The relationship between disease prevalence, incidence, and survival can be explored by use of the DISMOD II software, available free from the World Health Organization (http://www.who.int/healthinfo/boddismod/en/index.html).

Estimating Risk Factors

Discovering risk factors helps to identify who is most at risk of a disease, enables the development of strategies for primary and secondary prevention, and helps to understand the underlying pathologies. Risk factors for incidence are also risk factors for prevalence, so understanding the effects of risk factors will help to predict how the disease burden in a population will respond to demographic or cultural changes and to design interventions for primary prevention.

Although prospective population-based studies provide estimates of prevalence and incidence of dementia and are the most reliable means to estimate risk factors, they might not capture enough dementia cases or be detailed enough in their assessment of potential exposures. Where prospective studies are not feasible, retrospective studies, most commonly case control studies, are used to identify risk factors. In case control studies, the profile of exposure to risk factors is compared between a group with dementia and a control group. Case control studies have the advantage of being able to retrospectively examine multiple risk factors, but they can be biased because of their setting, the selection of the control group, or differential mortality.

Methodological Issues in Dementia Epidemiology

Dementia is a difficult disorder to study. In addition to the usual principles of epidemiology, there are several specific considerations when planning or assessing the quality and relevance of a study of dementia.

The definition of *dementia*, or of a particular subtype or specific symptoms of dementia, is not straightforward. Several commonly used definitions of *dementia* can identify substantially different subsets of the population (Erkinjuntti et al. 1997), and it is often impossible to distinguish among the major dementia subtypes on the basis of clinical characteristics. Similarly, cognitive and functional impairments, as well as behavioral and neuropsychiatric symptoms, each has many different definitions and corresponding instruments used for its assessment, each with its own strengths and weaknesses.

There are also specific measurement issues. Owing to the loss of cognitive function, visual or hearing impairments, or other disability, older persons are more likely to have difficultly completing questionnaires, and interviewers require specific training. Evidence regarding history of exposure to risk factors is subject to recall bias, particularly in retrospective studies. Proxy respondents, including caregivers or family members, may be used, but they might not be familiar with the history of the subject, and their responses might be influenced by other factors, including their relationship with the subject or their own point of view and cultural expectations.

The selection of both the target population to which the results of the study will be applied and the sample population from whom the study participants will be drawn is

important. The case-identification process and sampling strategy used can also affect results. Many older persons are institutionalized, and studies may be restricted to those still living at home or in a particular institutional setting. Some studies are conducted in atypically healthy populations, selected to have few comorbid conditions. The response rates of population-based studies and the way in which subjects are recruited are also important, because cognitively impaired persons may be less likely to participate. Identification of cases using existing health care services can bias results through the factors that lead people to arrive at psychiatric units, clinics, or general hospitals.

Two- or three-phase designs are common in studies of dementia in the population, where current diagnostic developments have led to the need for detailed and lengthy assessments. An initial basic screen, usually based on easily applied instruments for cognition such as the Mini-Mental State Examination (Folstein et al. 1975), is conducted to generate an enriched subsample of individuals, who then undergo a full assessment. Multiphase studies can be more efficient, but must be carefully analyzed so that estimates are applicable to the target population.

Dementia is strongly related to age even within the elderly population; therefore, where potential risk factors might also be age related, careful age adjustments are necessary. Case control studies of older persons are particularly subject to survival bias. For example, if a potential risk factor for dementia incidence reduces survival with dementia, then case control studies may discover a negative association between the risk factor and dementia, implying a protective effect, regardless of its true effect on dementia incidence.

In many studies of health, cognitive assessments are conducted, and a large number of outcomes and potential risk factors are recorded. Therefore, it is inevitable that false associations are occasionally discovered. Also, because positive results are published more frequently than negative results, a publication bias is likely to occur. Studies with entirely negative findings may not be reported at all. This bias can be compounded in systematic reviews and meta-analyses. Evidence should be considered more reliable when the finding was a stated aim of the investigation from which it was reported.

Exposures measured around the time of dementia incidence might be affected by the disease process itself, so exposures measured some time before dementia incidence may provide more reliable evidence.

Studies of the elderly population suffer from a higher rate of loss to follow-up than do studies of other populations. Dementia is a strong predictor of death, and in studies of dementia, it is possible for a significant number of participants to develop dementia and die in the interval between two assessments. Longitudinal studies must consider loss to follow-up as a potential confounder.

Cross-Cultural Studies

Cross-cultural studies of the risk factors for dementia contribute valuable information regarding a wide variety of different exposures and genetic diversity, and enable more accurate comparisons of the health care needs of different populations. They also present their own methodological difficulties. Foremost of these is the development of culture-fair instruments for the detection of dementia or other neuropsychiatric symptoms. Hendrie et al. (1996) discussed these issues and the insights gained in the context of three major cross-cultural studies of dementia.

Epidemiological Neuropathology

Epidemiological studies have revealed associations between many risk factors and dementia, with complicated interactions between various risk factors. Different risk factors are responsible for the buildup of neuropathology and its clinical manifestation as dementia. Epidemiological neuropathology—that is, the study of the distribution of neuropathology in the population and its association with dementia—is essential for understanding the mechanisms by which dementia could be prevented.

Epidemiological neuropathology is subject to many of the methodological difficulties of dementia epidemiology, and reliable estimates for the distribution of neuropathology and its interaction with dementia can only be obtained using population-representative samples, including persons with and without dementia. Because participants of population-based studies may not have been clinically assessed close to their death, a combination of their recent clinical assessment and retrospective information provided by informants must be used to determine their dementia status at death. Neuropathological data are usually available only at death, so the longitudinal assessment of its progression is not available, and it is difficult to make inferences about pathology in people who are alive.

A recent review identified only six studies of the neuropathology of dementia that were population based in both their sampling frame and case identification (Zaccai et al. 2006). These studies have challenged the idea that dementia occurs at definable thresholds of specific neuropathologies. Although a relationship between pathology and dementia is consistently observed, significant levels of neuropathology are often discovered in subjects without dementia, and dementia is often clinically present in subjects with little or no detectable pathology. For example, in a neuropathological study of people age 65 years and

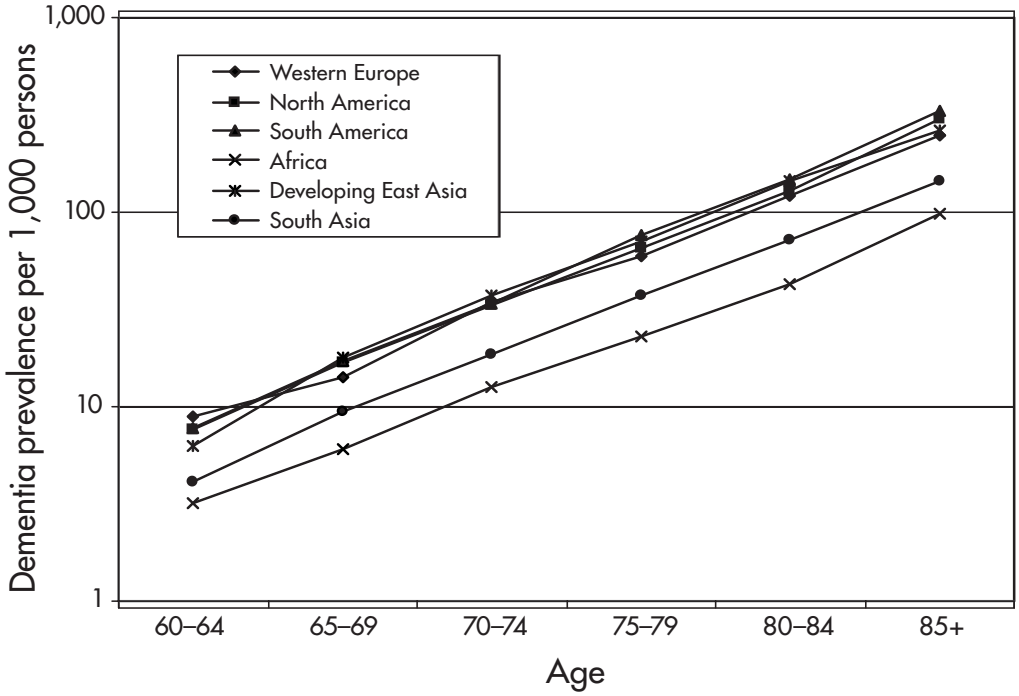

FIGURE 2–1. Geographic differences in age-specific dementia prevalence per 1,000 persons.
Source. Data from Delphi consensus study reported by Ferri et al. (2005).

older, 100 of whom had dementia and 109 who did not, researchers found neuropathology consistent with a diagnosis of probable or definite Alzheimer disease in 33% of nondemented participants (Medical Research Council Cognitive Function and Ageing Study 2001).

Global Prevalence and Incidence of Dementia

The quality and quantity of evidence regarding the prevalence of dementia vary enormously across the world. Western Europe, North America, and the developed West Pacific areas of Australia, Japan, and South Korea have had good-quality population-based studies from which reliable estimates of prevalence and incidence are available. In other areas, including India, China, Eastern Europe, West Africa, and South America, smaller localized studies exist from which population prevalence estimates can be extrapolated. However, no reliable evidence regarding the prevalence of dementia is available from several large, highly populated areas of the world, including Russia, Southern Africa, Indonesia, and much of South Asia; estimates for dementia prevalence in these areas currently rely on assumptions based on countries for which data are available.

A consensus study comparing dementia prevalence around the world was published using all evidence available in 2003 (Ferri et al. 2005). Some details about the studies and the estimates for prevalence used to reach the consensus estimates are available on the Alzheimer's Disease International Web site (http://www.alz.co.uk/research/consensus.html). The results of the consensus analysis are shown in Figure 2–1. An exponential increase in dementia prevalence with age is consistent throughout the world, although a substantial variation in the age-specific prevalence of dementia is evident across the world. The age-specific rates in South Asia and in parts of Africa are around 50%–60% and 30%–40%, respectively, of the rate in the developed world.

In 1998, a meta-analysis of dementia incidence studies was published that confirmed the exponential incrase in dementia incidence with age (Jorm and Jolley 1998). Studies from Europe, the United States, and Asia were compared. Similar rates were discovered in Europe and the United States, whereas the incidence in East Asia was lower. The use of different instruments for dementia diagnosis did not significantly affect the incidence rates, a finding supported by a later study in which similar incidence of dementia was found when two instruments were

TABLE 2–1. Age-specific incidence of dementia (with 95% confidence intervals), cases per 1,000 person years

Age	Meta-analysis of nine European studies (Jorm and Jolley 1998)		Adult Changes in Thought (Kukull et al. 2002)		MRC CFAS (Matthews et al. 2005)	
65–69	9.1	(6.5–12.7)	5.4	(8.0–13.5)	9.3	(5.6–14.2)
70–74	17.6	(14.2–21.9)	9.7	(6.5–13.5)	14.1	(9.6–22.0)
75–79	33.3	(29.0–38.3)	13.5	(29.3–44.7)	23.7	(17.4–30.7)
80–84	59.9	(52.8–67.9)	38.0	(44.5–72.9)	43.3	(33.5–54.3)
85–89	104.1	(84.6–128.2)	58.6	(74.7–156.7)	91.3	(72.6–109.9)
90–94	179.8	(129.3–250.1)	89.4	(57.8–127.9)		

Note. MRC CFAS=Medical Research Council Cognitive Function and Ageing Study.

directly compared in the same population (Riedel-Heller et al. 2001). Table 2–1 compares the age-specific incidence of dementia estimated in the nine Eruopean studies included by Jorm and Jolley (1998) with two more recent large incidence studies, the Adult Changes in Thought study in the United States (Kukull et al. 2002) and the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) in the United Kingdom (Matthews et al. 2005). Incidence estimates vary between studies but typically fall between 5 and 10 per 1,000 person-years in those age 64–69, between 10 and 20 per 1,000 in those age 70–74 years, between 15 and 30 per 1,000 in those age 75–79 years, and between 40 and 60 per 1,000 in those age 80–84 years. There is more uncertainty in the estimates of dementia incidence in the oldest old patients because of the smaller numbers and the high levels of dropout from studies through death or refusal in that age group.

While most studies of dementia prevalence focus on those age 50 years or older, a large population-based study of dementia in the young (Harvey et al. 2003) suggests that the exponential increase in dementia prevalence begins at least as young as age 30 years.

Risk Factors

Dementia is more prevalent in women than in men. A large amount of this difference is explained by the greater life expectancy of women and by a higher survival rate of women with dementia when compared with same-age men with dementia. The incidence of dementia is also slightly higher in women. A meta-analysis of European studies by the EURODEM incidence research group showed that women had a greater risk of developing dementia (odds ratio=1.2) (Andersen et al. 1999). More recently, results from a large prospective incidence study in the United Kingdom also showed an increased risk for women (odd ratio=1.6) (Yip et al. 2006).

Early-onset dementia is more common in individuals with a family history of dementia. In addition to its association with atherosclerosis, the apolipoprotein E (APOE) gene is acknowledged to be associated with dementia and, in particular, with a risk for Alzheimer disease. *APOE* has three major alleles, ε2, ε3, and ε4, leading to six common *APOE* genotypes. The risk of dementia is higher in heterozygous ε4 carriers than in those without an ε4 allele, and is higher still in those who are homozygous for ε4. An ε2 allele has been linked with a reduced risk of dementia. Estimates of the size of this association have been inconsistent, and it is thought that the effect of *APOE* depends on a variety of other factors, including age and ethnicity.

APOE allele distribution varies across the world. The ε4 allele is most common in areas of the world where the food supply is currently or has recently been scarce, and is lowest in southern Europe, the Middle East, and North Africa (Corbo and Scacchi 1999). This finding is consistent with research showing that *APOE* genotype determines the effects of dietary and other risk factors on the risk of dementia (Huang et al. 2005; Luchsinger et al. 2002).

The relationship between family history of dementia, *APOE* genotype, and risk of dementia was investigated in a 6-year prospective study in Sweden (Huang et al. 2004). Family history was a significant risk factor for dementia but only among carriers of the ε4 allele (relative risk was 1.9 when ε4 was present and 1.0 when ε4 was absent). Conversely, ε4 presence conferred a relative risk of 1.5 when there was no family history of dementia and of 2.6 in

people with a family history. These findings provide further evidence that the APOE gene moderates the extent to which other genetic or environmental factors affect the risk of dementia.

There are undoubtedly many undiscovered genetic influences on the risk of developing dementia. Advances in genomic technology have enabled the genome-wide search for genes that are associated with many diseases, including diseases that cause the dementia syndrome. Evidence regarding candidate genes for dementia is collected on the AlzGene database (www.alzforum.org) maintained by the Alzheimer's Research Forum (Bertram et al. 2007). In this text, rare genetic diseases that cause specific subtypes of dementia are discussed in Part III.

Modifiable Risk Factors

Individual studies have reported many associations between dementia and risk factors in early or middle years of life and risk factors near the time of dementia onset. Systematic reviews have been conducted, resulting in compelling evidence for some risk factors but inconsistent results for others.

Cerebrovascular disease is commonly observed in postmortem studies of persons with dementia, and therefore the risk factors that have been established for vascular disease are assumed to affect the risk of dementia. Vascular risk factors are also commonly associated with an increase in the risk of Alzheimer disease (Breteler 2000).

A 27-year prospective study of dementia incidence showed that after adjustment for comorbid conditions, midlife obesity (defined as a body mass index greater than 30 during ages 40–45 years) was a risk factor for dementia in old age (relative risk=1.74), and being overweight (body mass index of 25–30) also increased risk (relative risk =1.35) (Whitmer et al. 2005) . Adherence to a Mediterranean diet has been consistently associated with improved cardiovascular health and with a reduction in the risk of dementia (Scarmeas et al. 2006). Prospective studies have consistently associated oily fish consumption with a reduction in dementia risk (Barberger-Gateau et al. 2002; Huang et al. 2005).

Prospective studies have found that moderate intake of alcohol (specifically wine) is associated with a halving of dementia risk. However, the interactions between drinking, diet, and social activity are often not taken into account and may explain this association (Letenneur 2004, 2007).

Several prospective studies have reported an increase in dementia risk with low high-density lipoprotein (HDL) cholesterol and high low-density lipoprotein (LDL) cholesterol. High total cholesterol in midlife is also associated with increased dementia risk (Grodstein 2007). Prospective studies consistently report no difference in risk between individuals who use statin drugs and those who do not (Rea et al. 2005). Statin use is lower in persons with dementia, which may explain results from case control studies that suggested a protective effect and findings of less neuropathology among statin users (Li et al. 2007).

The Honolulu-Asia Aging Study explored the association between midlife hypertension and dementia (Launer et al. 2000). The risk of dementia was increased in those with untreated high blood pressure in midlife but not in those who had received treatment. However, a Cochrane review found no evidence that controlling blood pressure leads to a reduction in risk (McGuinness et al. 2006). Skoog and Gustafson (2002) reviewed the risk factors for hypertension and described possible mechanisms for its effect on the risk of dementia.

A systematic review found consistent evidence that diabetes both in midlife and later life is a risk factor for both Alzheimer disease and dementia in general (Biessels et al. 2006). Effective control of diabetes may reduce this risk.

The early controversy surrounding the effect of smoking on the onset of dementia has now been set aside, with prospective studies consistently finding either no effect (Doll et al. 2000; Yip et al. 2006) or evidence of increased risk of dementia or cognitive decline in smokers (Launer et al. 1999; Ott et al. 2004). Early case control studies had suggested that smoking might protect against dementia, but these findings can be largely explained by differential mortality effects (Almeida et al. 2002).

A case control study nested within a prospective population-based cohort study was used to explore the association between health in persons over age 60 years and incident dementia within 6 years. Stroke (odds ratio=2.1), Parkinson disease (odds ratio=3.5), and poor self-perceived health (odds ratio=3.9) were all found to be indicators for dementia (Yip et al. 2006).

Both current depression and a history of depression are associated with a doubling of the risk of dementia (Green et al. 2003; Jorm 2001). This increased risk is not explained by treatments for depression or by common risk factors.

The relationship between single traumatic head injury and dementia is unclear (Jellinger 2004). A meta-analysis of incidence studies in Europe by the European Community Concerted Action on the Epidemiology and Prevention of Dementia (EURODEM) Group found no increase in dementia risk with a reported history of head trauma (Launer et al. 1999). Boxing can lead to chronic brain injury, and heading a soccer ball has been implicated in brain injury and dementia, although the evidence for this relationship is inconsistent (Barnett and Curran 2003).

Social Activity, Education, and Cognitive Reserve

Cognitive reserve—the ability of the brain to sustain pathological damage without a decline in cognitive function—is thought to play an important role in the clinical manifestation of dementia. The explanation for this effect that is most consistent with current evidence is that cognitive reserve assists the brain to develop compensatory mechanisms to cope with the buildup of neuropathological damage. Several factors are thought to contribute to cognitive reserve, and evidence exists to link each with the risk of dementia. These factors include education, intelligence, occupation, and social interactions throughout life. A recent review (Valenzuela and Sachdev 2006) explored each of these domains in detail and found a summary odds ratio for the association of cognitive reserve and dementia of 0.54. The different domains are highly correlated; therefore, although it is accepted that cognitive reserve does play a role in preventing the clinical manifestation of dementia, the specific domains responsible for this effect, the mechanisms by which it occurs, and the potential for its use in prevention of dementia remain unclear.

Survival With Dementia

In a sample of 438 cases of incident dementia in the United Kingdom, median survival from diagnosis was 4.5 years (interquartile range: 2.8, 7.0). Age was a significant predictor of survival, with persons developing dementia in their late 60s surviving for a median of 10 years, compared with 5.4 years for people in their 70s, 4.3 years for people in their 80s, and 3.8 years for people age 90 years or older. After adjustment for age, mortality with dementia was higher in men than in women (hazard ratio=1.4).

Prevention and Treatment Trials

Recently, researchers have sought direct evidence that interventions through lifestyle changes or by active treatment can reduce the risk of dementia. Large prospective trials aimed at measuring the health effects of primary interventions are under way but have so far been unable to detect any reduction in dementia risk. Strategies for the prevention of dementia are discussed in Chapter 26, "Prevention of Dementia and Cognitive Decline."

Much treatment for dementia is aimed at secondary prevention—that is, at slowing or preventing decline in individuals diagnosed with dementia or with cognitive impairments that might lead to dementia. The issues that must be considered when assessing the evidence for a dementia intervention are similar to those for an epidemiological survey. The end points, whether they are objective measures of impairment, dementia severity, quality-of-life, or economic outcomes, need careful consideration. Studies of individuals with cognitive impairments are likely to suffer from noncompliance and loss of follow-up through deterioration or death.

Studies of secondary prevention require that a suitable target population be defined. This population consists of people diagnosed with mild dementia or with subthreshold levels of dementia symptoms. Mild cognitive impairment is the term often used to describe subthreshold dementia, although there are many competing definitions, and estimates for the efficacy of any intervention may be strongly influenced by the choice of definition.

The evidence for the efficacy of dementia treatments is discussed in detail in Part IV, "Treatment of Dementia."

Impact of Dementia

Dementia has an enormous impact on persons with the disorder and on those around them. The quality of life of individuals with dementia is affected by their cognitive and functional impairments, as well as the behavioral and psychological symptoms that often occur. These individuals also require increasing levels of care, which, together with the direct emotional impact of the disease, can lead to mental and physical health problems for caregivers and family members. The full-time and sometimes specialized care required for a person with dementia is expensive and has financial implications for caregivers and for health and social care services.

Many factors can affect the extent to which dementia has an impact on the lives of individuals with dementia and their caregivers. The natural history of dementia, including the rate of decline and the particular symptoms experienced, varies both across and within dementia subtypes. Also important are the premorbid personalities and the relationship between the person with dementia and his or her caregivers, and the health care, social, and financial support available to them. Interventions aim to reduce the overall impact of dementia. To assess the efficacy of interventions, measures are needed for the impact of dementia across the various areas.

In this section, we review the ways in which dementia affects the quality of life and comorbid health conditions of an individual and his or her caregivers, and also de-

scribe the financial burden to caregivers and the costs to both developed and developing economies. We review the evidence for the effect of the particular cognitive, functional, behavioral, and neuropsychiatric symptoms of dementia on the people it affects.

Impact on the Individual

Dementia affects every aspect of a person's life. By definition, it interferes with a person's autonomy, including the ability to live independently and to make choices and moral judgments. The decline in cognition and memory causes people to lose the activities they enjoy and damages personal relationships. In many cases, dementia also causes psychiatric problems, including depression and psychosis, and behavioral problems that lead to restrictions on personal freedom. In its later stages, dementia causes loss of motor control and prevents communication of a person's thoughts and feelings, including his or her wants and needs or medical symptoms the individual is experiencing. Dementia is also a factor in many comorbid conditions and is the leading predictor of death in the elderly (Tschanz et al. 2004).

Persons with dementia are vulnerable and may suffer physical, mental, or financial abuse. Cognitive deficits and lack of insight can lead to dangerous behavior and being exposed to various risks.

Quality of Life

The conceptualization and measurement of quality of life for persons with dementia has received increasing attention over the past 15 years, and various models and scales for its assessment have been described (Ettema et al. 2005; Ready and Ott 2003; Smith et al. 2005). Chapter 3, "Neuropsychiatric Assessment and Diagnosis," includes brief descriptions of two such scales, which are included as appendixes to this book. Appendix H is the Quality of Life in Alzheimer's Disease Scale (Logsdon et al. 1999). Appendix I is the Quality of Life in Late-Stage Dementia Scale (Weiner et al. 2000).

It is important to be able to measure the quality of life for people with dementia to enable the comparison of social and health care interventions. *Quality of life* is defined by the World Health Organization as "an individual's perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations and standards" (The WHOQOL Group 1995). Health-related quality of life (HRQoL) aims to measure the effect of a disease on a person's quality of life and is a concept applied to many health problems. Most models of HRQoL include a person's physical health, mental health, social and spiritual well-being, and autonomy. HRQoL measures are also used to calculate quality-adjusted life years, on which judgments regarding the cost-effectiveness of interventions may be based.

HRQoL is at least in part subjective, and traditional instruments for its measurement are difficult to apply to persons with dementia. Difficulties arise from patients' impaired memory of experiences, from language problems, and from lack of insight into their disabilities and environment. For these reasons, quality-of-life measures for individuals with dementia often rely heavily on objective components, such as a patient's level of impairment, the level of social interaction the person enjoys, and the quality of his or her surroundings. Proxy measures may also be used, although proxy reports have been shown to be unreliable after adjustment for objective measures (Shin et al. 2005). It is debated whether or not a single conceptualization or assessment of quality of life can be appropriate at all stages of dementia, because the difficulties in subjective assessment, as well as the domains of quality of life that are most affected by dementia, vary with dementia severity.

The model described by Lawton (1994) has been the basis for all recent developments in the conceptualization and assessment of HRQoL in persons with dementia. This model includes objective measures of the signs and symptoms of dementia as well as subjective components describing the experience from the patient's perspective. The most important difference between conceptualizations concerns how the various domains are included, in particular whether or not objective measures of impairment are regarded as predictors or indicators of quality of life.

Clinical studies of persons with dementia and informal interviews have been used to determine the specific domains of quality of life that are affected by dementia. These domains have subsequently been incorporated into formal HRQoL measures. Several reviews compare in detail the differing conceptualizations and assessments for quality of life in dementia and have identified a number of commonly included domains: behavioral competence, the care environment, social interaction and activities, and autonomy and independence (Ettema et al. 2005; Ready et al. 2003).

The domain of behavioral competence includes cognitive and functional abilities and is assessed using objective measures of the cognitive and functional impairments caused by dementia. Also included are behavioral disturbances that affect an individual's ability to live independently. The care environment of persons with dementia affects their quality of life. Persons with dementia are often moved from their homes into institutions, where they lose the ability to influence their surroundings. Neuropsychiatric symptoms that have a direct impact on quality of life are

common in dementia (see Chapter 15, "Psychiatric Disorders in People With Dementia"). These symptoms include affective disorders such as anxiety and depression, and psychotic symptoms such as hallucinations and delusions.

In the domain of social interaction and activities, impairments and loss of mobility can cause individuals with dementia to give up their work, hobbies, and other activities. In the later stages, it is important that people with dementia are able to participate in activities within their capacity. Relationships with family and friends often suffer as a direct result of impairments and neuropsychological symptoms, as a result of the burden of caregiving, and because of distance when the individual is institutionalized. Concern about socially inappropriate behavior can lead to avoidance of social situations. Dementia can cause a loss of empathy—the ability to understand the thoughts and behavior of others—which affects an individual's capacity for social interaction (Lough et al. 2006).

In the domain of autonomy and independence, persons with dementia may become increasingly dependent on others. Their decision-making capacity suffers, leading to legal and ethical issues (see Chapter 21, "Legal Issues," and Chapter 22, "Ethical Issues and Patterns of Practice"). Confidentiality with medical practitioners is compromised, and increasing dependence leads to an increasing invasion of privacy in many aspects of life by caregivers and service providers. The loss of control of many bodily functions affects personal integrity and dignity.

Each of the preceding domains can be measured objectively or subjectively in terms of the satisfaction of the person who has dementia with each aspect of his or her life. Subjective measures of quality of life also include measures of spirituality, morale, and self-esteem.

At present, little epidemiological information is available with respect to quality of life and dementia. Valid and reliable tools for its assessment have only recently become available, and most of the major longitudinal studies of aging and dementia do not include or have not reported quality-of-life outcomes. Consequently, there is a lack of information regarding the course in quality of life throughout the progression of dementia, and there are no data comparing quality of life for people with and people without dementia. On the other hand, clinical trials and cost-effectiveness studies are increasingly required to use quality-of-life measures as primary end points, and from these, as well as from field trials of quality-of-life instruments, associations with the severity of clinical symptoms are becoming available. Early evidence suggests that although the progression of cognitive and functional impairments affects objective aspects of quality of life, such as independent living and social activities, there is no consistent effect on subjective or proxy-rated measures of psychiatric well-being (Banerjee et al. 2006; Wlodarczyk et al. 2004).

The effect of specific neuropsychiatric symptoms on quality of life has been investigated (Banerjee et al. 2006; Shin et al. 2005). Depression, anxiety, irritability and agitation, and disinhibition are consistently shown to affect quality of life, whereas delusions, hallucinations, apathy, and sleep or appetite problems have not been found to have a significant effect.

Patient age is an important factor. The finding that older people with dementia report significantly better quality of life than younger people with dementia (Banerjee et al. 2006) may reflect the feeling that cognitive and functional impairments are an expected part of aging and affect older people less with respect to their expectations.

Two longitudinal studies of quality of life in dementia have been conducted (Lyketsos et al. 2003; Missotten et al. 2007). Both applied the Alzheimer's Disease–Related Quality of Life Scale (Rabins et al. 1999) at baseline, with follow-up interviews after 1 and 2 years. Both studies found that although there was no significant mean effect of dementia severity on quality of life with dementia progression, individual patients did experience important positive and negative changes during the follow-up periods. No explanations for these changes were found, but these studies confirm that factors other than worsening impairments are important determinants of quality of life.

Quality of Care

Dementia affects the health care provided to an individual. Patients with dementia often have trouble communicating their physical symptoms, and it is difficult for others to ascertain the patients' wishes or consent regarding treatments. A study of elderly care home residents found that those with dementia received less pain relief than those without dementia (Nygaard and Jarland 2005). A retrospective study of people who died following hospital admission found that fewer medical interventions were attempted in persons with dementia than in persons without dementia (Sampson et al. 2006).

A prospective study on the effect of health variables on incident dementia in the United Kingdom found that exposure to general anesthetic was inversely associated with a diagnosis of dementia within 6 years (Yip et al. 2006). This finding suggests that there are barriers to health care for elderly people with cognitive impairments that are even below the threshold for diagnosis of dementia. In the final stages of dementia, loss of motor function can mean that feeding and swallowing become difficult or impossible. (See Chapter 19, "Management of Advanced Dementia," and see Part V, "Caregiving, Legal, and Ethical Issues,"

for discussion of legal and ethical issues surrounding interventions used to prolong life.)

Vulnerability and Risk

Abuse or potentially harmful behavior toward persons with dementia by their caregivers is not uncommon, although it is difficult to accurately determine its prevalence because it is difficult to detect and because those who participate in studies in clinical settings are more likely to receive support services. Abuse can be measured objectively using the observer-rated Minimum Data Set Abuse screen, but this has been shown to be insensitive for persons with dementia (Cooper et al. 2008). More recently, a Modified Conflict Tactics Scale has been employed, which relies on interviews with caregivers to determine incidents of abusive behavior (Beach et al. 2005).

Of a sample of 86 caregivers of persons with dementia recruited as part of the London and the South East Region Alzheimer's Disease (LASER-AD) study (Cooper et al. 2008), incidents of abuse were identified in 24 cases (28%). Physical abuse was reported in three cases. A sample of 265 caregivers and care recipients from the Family Relationships in Later Life Study (Beach et al. 2005) found a similar rate of abusive behavior (26%), with the rate of physical abuse around 1%. Although the latter sample was not restricted to patients with dementia, it was found that increasing care-recipient need was a risk factor for abuse.

Of a consecutive series of 278 patients with Alzheimer disease recruited from a dementia clinic, 16% were reported by their caregivers to have behaved dangerously, compared with 2% of 45 control subjects without dementia. Those patients with impaired insight into their dementia had three times the risk of dangerous behavior (Starkstein et al. 2007).

When asked about the frequency of actual risk incidents, 69% of caregivers of a population-representative sample of 89 persons with Alzheimer disease reported at least one incident in the previous year (Walker et al. 2006). Falls were the most common (46%) incident, followed by wandering (38%); incidents involving fire, water, or electricity safety (33%); vulnerability to strangers (18%); and self-neglect (8%).

Comorbidity and Causes of Death

The dangerous behaviors described in the previous section have the potential to cause injury and illness to persons with dementia. Comorbidity may also be caused or worsened by lack of self-care, lack of both the awareness of symptoms and the ability to communicate symptoms, lack of motor function, malnutrition, and forgetting to take medication. It is debated whether or not people with dementia suffer more comorbid conditions than elders with other diseases. In a study of elderly patients attending primary care facilities, 107 patients with dementia were found to have the same comorbidity profile and overall number of comorbid conditions as 2,906 patients without dementia (Schubert et al. 2006). However, because comorbidity increases with dementia severity (Doraiswamy et al. 2002), it is likely that significant excess comorbidity is restricted to persons with severe dementia.

Maintaining oral health in patients with severe dementia is difficult, and oral health deteriorates as dementia severity increases. Poor oral health is linked to a reluctance to eat and may lead to malnutrition. In institutionalized older people, oral health is associated with pneumonia, which is the leading cause of death for persons with dementia (Yoneyama et al. 2002). Also, dementia has been reported to predict poor response to influenza vaccination (Bellei et al. 2006).

Studies of causes of death are based on autopsies, death certificates, or studies of illnesses that patients had in the time immediately before their death. On death certificates, dementia may be reported as an underlying cause of death or mentioned as a contributing factor to an independent cause. However, even when dementia is present, it is often not recorded on death certificates, so mortality statistics grossly underestimate dementia in the population. Nevertheless, when it is recorded, it can provide valuable information on comorbidity at death.

To determine the associations between dementia and other recorded causes of death in older adults, Wilkins et al. (1999) conducted an analysis of 113,000 death certificates that reported data on multiple causes of death. Dementia was given as the primary cause of death on 2% of records and mentioned as a contributing factor on 6%. Pneumonia and influenza, as well as some cerebrovascular diseases, were significantly associated with a mention of dementia on death certificates. Associated causes of death arising directly from the effects of cognitive impairments included malnutrition, symptoms of the digestive system, chronic skin ulcers, accidental injury, fractures, obstruction of the respiratory tract, and suffocation.

Pneumonia in the week before death affected 53% of people who died with advanced dementia in a long-term-care facility (Chen et al. 2006). In a review of autopsy reports at an academic medical center, pneumonia was found in 24 (46%) of 52 persons who died with dementia (Fu et al. 2004).

A study of primary causes of death in enrollees with dementia in the Cardiovascular Health Study (Fitzpatrick et al. 2005) reported a lower rate of death from pneumonia (10%), although dementia itself was given as the cause of death in 19%. Cerebrovascular disease was considered the

primary cause of death in 14 (42%) of the 33 people diagnosed with vascular dementia.

Suicide, Withdrawal of Treatment, and Euthanasia

Psychotic symptoms are common in dementia. A case series of seven patients with dementia admitted to a geriatric psychiatry unit following attempted suicide found that delusions were the main cause of the attempt in all cases (Tsai et al. 2007). Depression is common in early-stage dementia, which may confer an increased suicide risk, but little evidence is available to support this possibility. Suicide has been anecdotally reported as a response to a diagnosis of dementia (Ferris et al. 1999).

Most jurisdictions do not allow euthanasia or physician-assisted suicide, although the withdrawal of life-prolonging treatment is practiced in many areas. The ethics of the continuation of life-prolonging treatment in advanced dementia is discussed in Chapter 22 of this volume.

Where euthanasia is legal, the competence of the patient is an important issue. In the Netherlands, physicians are allowed to perform euthanasia for patients with dementia based on advance directives written while the patient was still competent, although the acceptability of advance directives is controversial and, in practice, physicians rarely comply. A recent survey of 410 physicians in the Netherlands revealed that of 114 cases where an advance directive was evident, only five directives were ultimately carried out (Rurup et al. 2005). In Oregon, which has enacted the Death with Dignity Act, advance directives cannot be used to request euthanasia.

Impact on Caregivers

Much of the impact of dementia falls on the caregivers of the patients (Burns 2000). Informal dementia care is delivered primarily by spouses or adult children, who usually have no training or prior experience in caregiving. In the case of progressive dementias, the requirements of care steadily change. Dementia care is time-consuming and has a high economic cost for caregivers, as discussed later in this chapter and in Chapter 20, "Supporting Family Caregivers."

The primary stressor for a caregiver of a person with dementia is the demand of the care itself. The neuropsychiatric and behavioral problems that are common in dementia also cause stress for caregivers. A significant proportion of dementia patients demonstrate aggressive behavior (see Chapter 15 of this volume), and caregivers can feel physically threatened and concerned about taking charge of the patient, for example, when limiting the patient's independence to prevent exposure to harm. Informal caregivers who are close to the dementia patients suffer from the emotional impact of the disease, as well as from the responsibility of caregiving.

Secondary stressors arise from aspects of caregivers' lives that are affected by their caregiving duties. These include financial problems caused by the cost of dementia and the necessity for caregivers to reduce their hours of paid work. The demands of caregiving can lead to missed opportunities for the caregiver, as well as social withdrawal, family conflicts, and difficulties with other relationships.

Appraisal or subjective stress is the burden that caregivers place on themselves and is related to how well they feel they are fulfilling the caregiving role. Caregivers often feel confused and unsure about the actions they should take and the services available to them. Because support from various health care and social services is often fragmentary, caregivers often become care coordinators despite their lack of knowledge of dementia or the options available to them.

Other factors moderate the burden on caregivers by altering the primary stressors, the way in which these lead to secondary stressors, or the caregivers' appraisal of their situation. They include characteristics of the patient, the caregiver, and the quality of their preexisting relationship, as well as the support and interventions available to them.

Caregivers commonly suffer from physical and psychological problems. Hypertension, stress, poor self-care, diet, loss of sleep, impaired immune function, depression, and relapse of previous psychiatric disorders have been reported (Burns 2000). Stress and negative reactions in caregivers can increase the risk of problematic behavior in patients. Also, caregiver burden has been shown to increase the risk of abusive behavior toward the care recipient (Beach et al. 2005).

The burden of caregiving for dementia patients is well studied, and measures to capture the effect on caregivers have been developed for use in epidemiological studies and intervention trials. These include subjective and objective measures of health-related quality of life, mortality statistics, and health care service utilization.

There are several ways in which measures of the burden of care can be applied. Cross-sectional studies can measure the burden of caregiving for a person with dementia versus caregiving for a person without dementia. Alternatively, the health status of caregivers can be compared with age- and sex-adjusted norms for their populations, although exposure to risk factors common to both the caregiver and care recipient might cause the health of caregivers to be worse than that of their peers without caregiving responsibilities. Furthermore, there is evidence that those at risk of becoming caregivers already

suffer poorer health and more social isolation than their peers, so the effect of caregiving on the health of individuals should be assessed using longitudinal studies.

Mental and physical HRQoL scores were measured in 2,477 caregivers of patients with Alzheimer disease (Markowitz et al. 2003). Caregivers had lower-than-normal, age-adjusted mental scores at all ages, and those age 54 years or younger also had lower age-adjusted physical scores. Caregivers had better mental health scores when better social support was available, when their perceived quality of patient care was higher, and when patients needed fewer hours of care and had fewer behavioral symptoms. Caregivers' physical health was better when their perceived quality of patient care was higher and when the patients exhibited fewer behavioral symptoms.

Caregiving also increases mortality. Results from the Caregiver Health Effects Study showed an increased risk of 4-year mortality for caregivers (Schulz and Beach 1999), with caregivers of a disabled spouse 1.5 times more likely to die within 4 years than their peers whose spouse was not disabled.

Economic Impact of Dementia

The costs associated with dementia arise primarily from care requirements, direct treatment costs, and excess medical costs caused by comorbidity. There is also a considerable cost to the economy from caregivers and patients leaving the workforce, as well as increased care they themselves may need as a result of the impact of caregiving. Costs are shared between the person with dementia and his or her caregivers, health care services, the voluntary sector, and various government agencies. The exact distribution of costs varies according to the model for health care in a particular area and may depend on patients' ability to pay for their own care and treatment, the resources available to local health care services, and local assessments of the cost-effectiveness of specific interventions.

Economic costs are estimated by combining the costs estimated using samples of dementia patients with estimates of dementia prevalence. Most studies of the cost of dementia have been undertaken in developed counties. Cost estimates vary over time with wages, and varying exchange rates make comparisons across countries difficult. Wimo et al. (2007) produced an estimate for the total societal costs of dementia in each country in the world in 2005. They estimated that the global cost of dementia, including medical expenditures and informal care costs, was $315 billion in U.S. dollars, which corresponds to $49 for each of the world's population. Constant age-specific prevalence around the world was assumed, leading to an estimate of 29.3 million people with dementia in 2003. Recent evidence (see "Epidemiology" section in this chapter) suggests that this may result in an overestimate for Africa and South Asia.

Costs to Health Care Service

Of the estimated $315 billion global cost of dementia, $210 billion was the estimated direct cost of health care. In North America, the cost of health care services for individuals with dementia was estimated to be $60 billion, corresponding to $17,700 per person with dementia, or $180 for each member of the population (Wimo 2007). A recent review estimated that the annual cost of dementia in Europe varied from 6,000 to 19,000 euros per patient, although methodological differences were present between cost evaluations in different countries (Jonsson and Berr 2005).

Persons with dementia make up a large proportion of the hospital population, and the cost of excess hospitalization is a significant proportion of the cost of their care. Records from the Johns Hopkins Hospital revealed that although the prevalence of dementia among discharged patients was similar to that in the surrounding community, the mean length of stay for a dementia patient was 10.4 days compared with 6.5 days for patients without dementia, leading to excess costs of around $4,000 (at year 2000 prices) per patient per visit (Lyketsos et al. 2000). In the United Kingdom, it is estimated that 20% of the beds in general hospitals are occupied by individuals with dementia (Royal College of Psychiatrists 2005).

Not all of the medical costs for persons with dementia are caused by their dementia. A comparison of medical expenses of Medicare beneficiaries found that dementia was associated with an excess cost of $6,927 (at 1999 prices), corresponding to 3.3 times the medical expenditure of patients without dementia (Bynum et al. 2004).

Cost of Informal Care

Models for the cost of informal caregiving are based on estimating the hours of care provided. This cost can then be described either as an opportunity cost in terms of loss of earnings or as an estimate of what it would cost to replace informal care with professional care (i.e., the value of the care provided).

A detailed model of the time and financial costs of caregiving for dementia in the United States revealed the extent to which the level of required care depends on dementia severity (Langa et al. 2001). The number of informal caregiving hours provided to each person with dementia increased from 8.5 per week in mild cases to 17.4 per week in moderate cases to 41.5 per week in severe cases.

The National Longitudinal Caregiver Study (Moore et al. 2001), one of the few national studies of caregiving in the United States, provided estimates of the cost of caregiving in terms of the value of caregiving, the loss of earnings, expenses to caregivers associated with formal caregiving services, and caregivers' own excess health care costs. In addition to the costs associated with the hours of care required, this study revealed that caregivers spent an average of $4,500 annually out of pocket for a range of formal health services. Caregiver excess health care utilization was almost zero, although caregivers are known to have worse health than those without caregiving responsibilities. This suggests that caregivers do not tend to seek medical help for themselves, potentially causing a longer-term health problem after the caregiving role has ended. This study is not representative of the U.S. population because the study sampled female caregivers of male veterans who have better health care coverage than most.

Zhu et al. (2006a), based on the results of a longitudinal study of patients recruited at an Alzheimer disease clinic, reported that around 80% of individuals with dementia receive informal care, with the proportion receiving informal care not affected by severity. The hours of care per week for those receiving care increased from 28 at baseline to 53 at year 4, at a cost of $20,500 at baseline to $43,000 in year 4.

Indirect Cost to the Economy

In a report for the Alzheimer's Association, Koppel (2002) described the cost of dementia to U.S. businesses. The cost was broken down as follows: the cost of caregivers leaving their employment, the productivity loss associated with caregiver absenteeism, the cost of insurance for caregivers on leave, the cost of employing temporary workers, and the direct cost of medical care provided by businesses. The total indirect economic cost in 2002 was estimated as $61 billion.

From the National Longitudinal Caregiver Study mentioned earlier (Moore et al. 2001), it was estimated that 60% of caregivers reduce working hours because of caregiving, 42% reported being late for work because of caregiving, and 39% had taken sick leave. Half of the persons who had retired reported that caregiving responsibilities were the main reason for their retirement.

Cost of Dementia and Severity of Clinical Symptoms

The cost of care increases with dementia severity. More detailed investigations have been made to examine the contribution to the cost of care conferred by varying levels in the cognitive, functional, neuropsychiatric, and behavioral aspects of dementia. The Resource Implications Study of MRC CFAS estimated the total health care costs associated with dementia in England and Wales (McNamee et al. 2001). A model was developed for the effect of level of cognitive and functional impairment. Costs increased by 15% per 1-point decrease in Mini-Mental State Examination score and by 9% per point on an activities of daily living scale.

A longitudinal study of patients recruited from dementia clinics was used to study the effect of dementia severity on direct medical and care costs and on informal care costs (Zhu et al. 2006b). Direct care costs increased by 7.7% per point increase on the Blessed Dementia Rating Scale (BDRS), and informal costs were increased by 5.4% per BDRS point. After adjustment for severity, women have 21% less direct care cost than men. Hospitalization accounted for about one-third of the total cost. In addition to expenses due to cognitive and functional impairments, neuropsychiatric symptoms of dementia increase the cost of care by $343 per year per point on the Neuropsychiatric Inventory (Murman and Colenda 2005).

The association between hospitalization and dementia severity differs between patients living at home and those living in institutions. Patients living at home are hospitalized more frequently with increasing dementia severity, whereas those living in institutions are hospitalized less often and with a reduced length of stay and cost per admission as severity increases (Fillenbaum et al. 2001). This might reflect a difference in the patients who are institutionalized compared with those who are not, but also the experience of and ability of institutions to prevent comorbidity and provide medical care.

Cost-Effectiveness

The cost-effectiveness of a treatment is measured as a combination of the treatment cost, the costs or savings that use of the treatment confers elsewhere, and the health utility to individuals with dementia and their caregivers. Because cost-effectiveness studies are used by health care providers to determine the treatments that are made available to patients, their methodology and results can be subject to intense public scrutiny.

Health utility is measured in quality-adjusted life years, which requires a measure for health-related quality of life and weights that describe the adjustment comparing quality-impaired life to years of life in full health. Estimates for cost savings can be made directly by including cost as an outcome of an intervention trial, but they are more commonly modeled by combining estimates of the

association between the cost of care and severity of clinical symptoms with the efficacy of the intervention. Models for cost savings typically include factors such as the effect of the severity of clinical symptoms on the level of care required, the time to institutionalization of the patient, and the effect on survival.

Owing to the high cost of caring for someone with moderate or severe dementia and the strong association between the cost of care and the levels of impairments, interventions for dementia may provide an overall cost benefit even before the improvement in health utility is considered.

Impact on the Developing World

The term *developing world* is used to encompass areas that have an enormous variety of cultural and economic situations; these areas include Latin America, Eastern Europe, the Middle East, Africa, and much of Asia. In the context of the discussion of dementia, the developing world is defined as those areas that have low awareness of dementia as a disease or that lack health care or support services for persons with dementia and their caregivers. This corresponds closely with less economically developed areas. The World Health Organization estimates that after ischemic heart disease, cerebrovascular disease, and depression, dementia is the fourth leading cause of burden of disease in the developing world, causing 5% of all disability-adjusted life years lost (Lopez et al. 2006). Despite this, and owing to the lack of awareness and infrastructure, dementia remains understudied in the developing world. Until recently, very few studies of the epidemiology of dementia, the circumstances of persons with dementia, or its social or economic impact had been set in developing populations.

To address this lack of awareness, Alzheimer's Disease International held a conference in 1999 with 400 delegates from developing and developed nations, a result of which was the formation of the 10/66 Dementia Research Group. The consensus statement of the aims of this group (Prince 2000) sets out the important research questions that need to be addressed, their priorities, and the appropriate research methodology. Important considerations include the ways in which dementia research in the developed world should be disseminated and used to inform policy; the need and potential for collaboration between developing and developed nations in creating consistent, culture-fair assessments; the need for accurate prevalence estimates for each country; and the potential for studying regional variation to generate hypotheses regarding the causes of dementia. Emphases include describing the circumstances and care arrangements of persons with dementia, the impact of dementia on caregivers and the community, and the need for longitudinal assessment.

Pilot studies to determine the care arrangements for persons with dementia and the burden of care were conducted in 24 centers across India, China, Southeast Asia, Latin America, the Caribbean, and Africa (Prince 2004). It was found that females within the family undertake much of the informal care. Multigenerational households and larger extended families are common, but this does not reduce the caregiver burden on the primary caregiver. There is less use of care homes, so the family takes more of the burden of care in later stages. Most government health care in the developing world is focused on treatable acute problems, and not much treatment or support is available for patients with dementia. Consequently, a higher proportion of gross national product in the form of family income is spent on private medicine for dementia patients than is spent in the developed world. Many informal caregivers have to leave or reduce their paid employment but with less financial support than is available to caregivers in the developed world.

In the areas studied, 25%–50% of the households included children. The time and resources spent caring for an elderly family member with dementia has a direct impact on the care and education of the younger family members. Dementia in parts of the world with less social or medical support is contributing to the cycle of deprivation suffered in poor communities.

Trends in Prevalence and the Future of Dementia Epidemiology

Because the population of the world is aging, the prevalence of dementia is increasing. The future prevalence of dementia can be projected using predictions of the age structure of a population combined with age- and region-specific prevalence estimates. Figure 2–2 shows estimates for the risk of dementia in various parts of the world in 2001, 2020, and 2040 using this approach (Ferri et al. 2005).

Other factors will affect the future age-specific prevalence of dementia. These include changes in the age-specific incidence of dementia and in the average length of survival with dementia. Because the risk of dementia in an individual is known to be influenced by modifiable risk factors, the rate in the population will vary in response to varying patterns of exposure to risks. However, these patterns are complicated and almost impossible to predict. Evidence from prospective incidence studies using co-

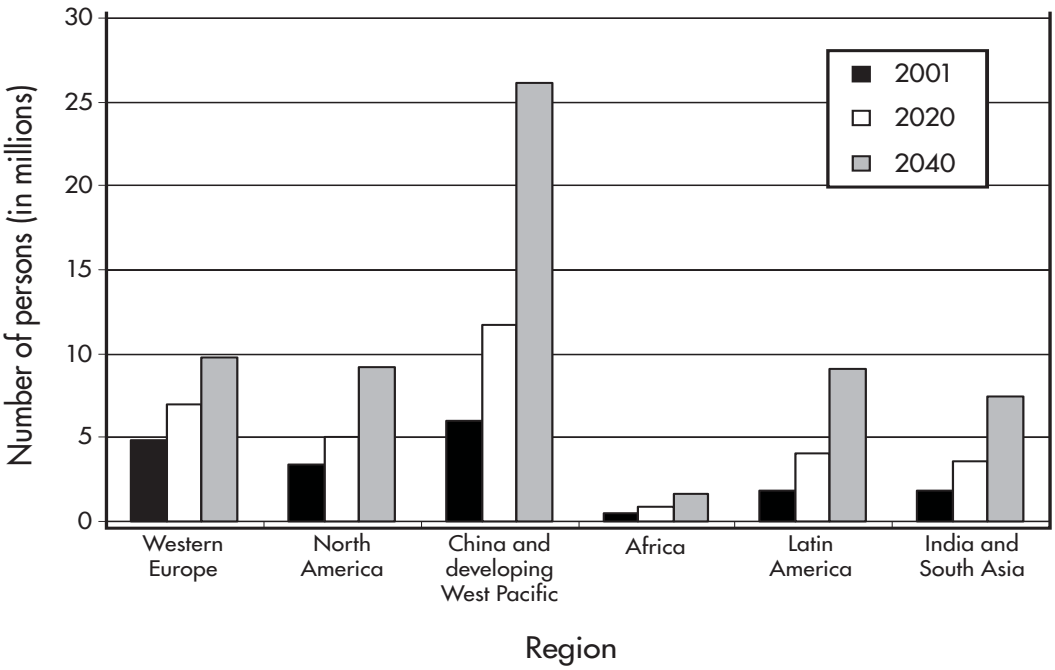

FIGURE 2–2. Estimated numbers of persons (in millions) with dementia in selected regions of the world in 2001, with projections for 2020 and 2040.
Source. Data from Delphi consensus study reported by Ferri et al. (2005).

horts of varied ages enables an examination of past changes in the incidence of dementia. Exposure to risk factors in midlife is known to affect the risk of dementia; therefore, it is the current prevalence of risk factors that will determine the burden of dementia in the coming decades. An increase in the incidence of dementia is also likely to arise from an increase in the rate of survival from vascular disease.

Developments in interventions aim to reduce the burden of dementia but might have the effect of extending survival, thereby increasing its prevalence. Interventions aimed at secondary prevention aim to delay the onset of dementia; if successful, these have a great potential to reduce dementia prevalence. In many parts of the developing world, changes in lifestyle and age structure, combined with poor awareness of health issues, are likely to lead to the greatest rise in dementia prevalence.

Future Priorities for Dementia Epidemiology

Given the accumulating evidence that modifiable risk factors might affect dementia risk, an immediate priority for dementia epidemiology is to determine the extent to which the prevalence of dementia can be influenced by public health policy and primary prevention. This can be achieved only through large, long-term, primary prevention trials following populations though young and middle ages, and these trials present their own methodological difficulties. Population-based studies of dementia should include measures of quality of life, to enable comparisons between people with dementia and their nondemented peers and to discover the factors that affect quality of life in the population with dementia. Epidemiological neuropathology is in its infancy, and very little is known regarding the clinical consequences of specific neuropathological features or the ways in which neuropathology is affected by known risk factors for dementia. Large population-based prospective neuropathological studies including detailed clinical assessments before death are needed.

It is possible that highly effective treatments will become available for the primary or secondary prevention of dementia and will benefit a large proportion of the population. If so, the public demand for such treatments will be great, and it is essential that high-quality population-based epidemiology is available to inform policies regarding costs and benefits. Epidemiological and health economic controversies will inevitably occur, and it is crucial that all methodology be rigorous, transparent, and based on evidence of the highest quality.

KEY POINTS

- Prospective population-based studies of dementia provide the most reliable epidemiological evidence. There are many important methodological considerations when planning or evaluating an epidemiological study of dementia.
- Age is the most important risk factor for dementia incidence, and there is evidence that the risk is affected by genetic factors, cognitive reserve, and exposure to risk factors both in midlife and old age.
- Despite evidence that modifiable risk factors affect the risk of dementia, primary and secondary prevention trials are needed to assess the potential benefit of treatments or public health interventions.
- The impact of dementia can be measured in terms of the quality of life of persons with dementia and their caregivers; however, measures of quality of life in dementia are controversial and are not yet widely used in studies of dementia epidemiology.
- The impact of dementia depends on the clinical characteristics and personalities of the person with dementia and his or her caregivers, as well as the availability of support services.
- Dementia in the developing world is understudied despite the enormous burden of disease it causes. Epidemiological studies of dementia in the developing world are under way and will provide important information to reduce the impact of dementia and provide valuable cross-cultural insights.
- Dementia has an economic impact on individuals, health care services, and the wider economy. Evaluating the cost of dementia is important for planning social and health care services and to inform models of cost-effectiveness of treatments.

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PART II

Evaluation and Diagnosis of Dementia

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CHAPTER 3

Neuropsychiatric Assessment and Diagnosis

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The assessment of individuals with cognitive impairments or cognitive complaints includes a thorough review of potential medical, neurological, and psychiatric causes of cognitive dysfunction. Cognitive dysfunction may occur at any age but becomes increasingly common in older adults and manifests in many ways, including memory slips, inappropriate social behavior, suspiciousness, perceptual distortions, poor hygiene, and hoarding. Mild levels of cognitive inefficiency appear to be part of the average aging process, but more severe impairments in cognitive spheres such as memory, language, and judgment often herald the onset of diagnosable cognitive disorders.

In this chapter, we review the DSM-IV-TR (American Psychiatric Association 2000) cognitive disorders, other cognitive syndromes, and other psychiatric disorders that may confound the diagnosis of cognitive disorders. This material anticipates Chapter 4, "Medical Evaluation and Diagnosis," and Chapter 15, "Psychiatric Disorders in People With Dementia." This chapter covers these topics: normal cognitive aging, cognitive disorders that do not meet DSM-IV-TR criteria, psychiatric disorders with cognitive symptoms, techniques of neuropsychiatric assessment, evaluation of speech and language, and scales for detecting and rating cognitive and neuropsychiatric phenomenology.

DSM-IV-TR Cognitive Disorders

DSM-IV-TR diagnoses are symptom clusters that meet a threshold of "clinically significant distress or impairment in social, occupational, or other important areas of functioning" (American Psychiatric Association 2000, p. 8). Thus, many persons with early dementing diseases do not

meet DSM-IV-TR criteria for dementia. The advantage of threshold diagnoses over disease diagnoses is that the former are less likely to yield false-positive diagnoses. On the other hand, threshold diagnoses do not detect early disease and thus may delay possible disease-modifying treatments. Despite these shortcomings, it is important to make diagnoses by criteria that are stable and reproducible and that reflect the functional impact of diseases.

Increasingly, the goal for diagnosis of cognitive disorders has become early detection so that they can be treated before they evolve to dementia. For this reason, clinicians are now more likely to diagnose Alzheimer disease before symptoms meet full criteria for DSM-IV-TR dementia of the Alzheimer type. In addition, many disorders that lead to dementia do not begin with impaired memory. For example, patients with frontotemporal dementias may present first with deficits in language or in executive function. Furthermore, despite the restriction of the definition of dementia as a cognitive disorder, it is apparent that behavioral and emotional symptoms are intrinsic to the diseases underlying the cognitive disorders and are not simply emotional reactions to them (Finkel et al. 1996).

As indicated in Chapter 1 of this volume, "Dementia and Alzheimer Disease: Ancient Greek Medicine to Modern Molecular Biology," earlier versions of DSM (DSM-I through DSM-III-R; American Psychiatric Association 1952, 1968, 1980, 1987) contained the category of organic mental disorders, described as constellations of cognitive, behavioral, and emotional symptoms thought to result from demonstrable changes in brain anatomy or physiology. Although the functioning of mental processes was thought to be abnormal in both organic disorders and functional disorders, the underlying brain anatomy and physiology were considered to be normal in organic disorders. It is now apparent that mental disorders are accompanied by altered brain activity, making distinctions between *organic* and *functional* perhaps superfluous and misleading. For these reasons, DSM-IV and DSM-IV-TR replaced the former diagnostic category of organic mental disorders with these: delirium, dementia, and amnestic and other cognitive disorders; mental disorders due to a general medical condition; and substance-related disorders (see Table 3–1) (American Psychiatric Association 1994, 2000).

The cognitive disorders are overlapping symptom complexes that often manifest in the course of the same underlying disease. For example, an evolving Pick disease might be diagnosed first as a personality change due to a general medical condition. As the patient's executive function and information processing become more impaired, the disorder would become diagnosable as a dementia. Many times, several disorders affecting mental function coexist. Persons with cognitive impairment often become delirious. Major depression may coexist with dementia. Persons with Down syndrome often develop Alzheimer disease (Lott and Head 2005). Also, a dementing illness may complicate schizophrenia or bipolar disorder.

Despite the limitations of DSM-IV-TR, diagnosis of DSM-IV-TR mental disorder subtype is important. In some cases, proper diagnosis is a life-or-death issue, as in differentiating barbiturate withdrawal or acute Wernicke syndrome from a dementia.

Normal Cognitive Aging

How does one differentiate normal aging from pathological cognitive decline? Finding an answer to this question is important to many persons concerned about changes in their own cognitive functioning or the functioning of a loved one and is of paramount significance for early intervention. Research in normal aging is complicated by the paucity of longitudinal studies, which are rare because of their complicated logistics and cost. The more common type of study compares different age groups, but such studies are confounded by cohort effects, such as differing life experiences, nutrition, education, and the selective attrition of elders. Another confound in comparative studies is the influence on cognition of diseases such as hypertension and diabetes. Controlled studies that exclude persons with such conditions find less difference between younger adults and older adults. In one such study, healthy adults age 50–82 years were able to learn word lists as well as younger adults did (Gunstad et al. 2006). Nevertheless, it is clear that although vocabulary and general knowledge remain stable with aging, speed of information processing and psychomotor performance decline with normal aging.

Memory

Impaired memory is more prevalent in older adults than younger adults (reviewed in Connor 2001). In a survey of memory function performed among community-dwelling elderly persons as part of the 2000 U.S. census, individuals were rated as having moderate to severe memory problems if they recalled four or fewer words from a list of 20 words on combined immediate and delayed recall. Based on this criterion, 4% of individuals between ages 65 and 69 years and 36% of those age 85 years or older had moderate to severe memory problems (Federal Interagency Forum on Aging Related Statistics 2000).

TABLE 3–1. DSM-IV-TR classification of delirium, dementia, and amnestic and other cognitive disorders; mental disorders due to a general medical condition not elsewhere classified; and substance-related disorders

Delirium, Dementia, and Amnestic and Other Cognitive Disorders

DELIRIUM

293.0 Delirium Due to . . . *[Indicate the General Medical Condition]*
——.– Substance Intoxication Delirium *(refer to Substance-Related Disorders for substance-specific codes)*
——.– Substance Withdrawal Delirium *(refer to Substance-Related Disorders for substance-specific codes)*
——.– Delirium Due to Multiple Etiologies *(code each of the specific etiologies)*
780.09 Delirium NOS

DEMENTIA

294.xx Dementia of the Alzheimer's Type, With Early Onset *(also code 331.0 Alzheimer's disease on Axis III)*
.10 Without Behavioral Disturbance
.11 With Behavioral Disturbance
294.xx Dementia of the Alzheimer's Type, With Late Onset *(also code 331.0 Alzheimer's disease on Axis III)*
.10 Without Behavioral Disturbance
.11 With Behavioral Disturbance
290.xx Vascular Dementia
.40 Uncomplicated
.41 With Delirium
.42 With Delusions
.43 With Depressed Mood
Specify if: With Behavioral Disturbance

Code presence or absence of a behavioral disturbance in the fifth digit for Dementia Due to a General Medical Condition:

0 = Without Behavioral Disturbance
1 = With Behavioral Disturbance

294.1x Dementia Due to HIV Disease *(also code 042 HIV on Axis III)*
294.1x Dementia Due to Head Trauma *(also code 854.00 head injury on Axis III)*
294.1x Dementia Due to Parkinson's Disease *(also code 331.82 Dementia with Lewy bodies on Axis III)*
294.1x Dementia Due to Huntington's Disease *(also code 333.4 Huntington's disease on Axis III)*
294.1x Dementia Due to Pick's Disease *(also code 331.11 Pick's disease on Axis III)*
294.1x Dementia Due to Creutzfeldt-Jakob Disease *(also code 046.1 Creutzfeldt-Jakob disease on Axis III)*
294.1x Dementia Due to . . . *[Indicate the General Medical Condition not listed above] (also code the general medical condition on Axis III)*
——.–– Substance-Induced Persisting Dementia *(refer to Substance-Related Disorders for substance-specific codes)*
——.–– Dementia Due to Multiple Etiologies *(code each of the specific etiologies)*
294.8 Dementia NOS

AMNESTIC DISORDERS

294.0 Amnestic Disorder Due to . . . *[Indicate the General Medical Condition]*
Specify if: Transient/Chronic
——.– Substance-Induced Persisting Amnestic Disorder *(refer to Substance-Related Disorders for substance-specific codes)*
294.8 Amnestic Disorder NOS

OTHER COGNITIVE DISORDERS

294.9 Cognitive Disorder NOS

Mental Disorders Due to a General Medical Condition Not Elsewhere Classified

293.89 Catatonic Disorder Due to . . . *[Indicate the General Medical Condition]*
310.1 Personality Change Due to . . . *[Indicate the General Medical Condition]*
Specify type: Labile Type/Disinhibited Type/Aggressive Type/Apathetic Type/Paranoid Type/Other Type/Combined Type/Unspecified Type
293.9 Mental Disorder NOS Due to . . . *[Indicate the General Medical Condition]*

Substance-Related Disorders

The following specifiers apply to Substance Dependence as noted:

[a]With Physiological Dependence/Without Physiological Dependence
[b]Early Full Remission/Early Partial Remission/Sustained Full Remission/Sustained Partial Remission
[c]In a Controlled Environment
[d]On Agonist Therapy

The following specifiers apply to Substance-Induced Disorders as noted:

[I]With Onset During Intoxication/
[W]With Onset During Withdrawal

ALCOHOL-RELATED DISORDERS

Alcohol Use Disorders

303.90 Alcohol Dependence[a,b,c]
305.00 Alcohol Abuse

Alcohol-Induced Disorders

303.00 Alcohol Intoxication
291.81 Alcohol Withdrawal
Specify if: With Perceptual Disturbances
291.0 Alcohol Intoxication Delirium
291.0 Alcohol Withdrawal Delirium

TABLE 3–1. DSM-IV-TR classification of delirium, dementia, and amnestic and other cognitive disorders; mental disorders due to a general medical condition not elsewhere classified; and substance-related disorders *(continued)*

Substance-Related Disorders *(continued)*

Alcohol-Induced Disorders *(continued)*
291.2 Alcohol-Induced Persisting Dementia
291.1 Alcohol-Induced Persisting Amnestic Disorder
291.x Alcohol-Induced Psychotic Disorder
291.0 Alcohol Withdrawal Delirium
.5 With Delusions[I,W]
.5 With Hallucinations[I,W]
291.89 Alcohol-Induced Mood Disorder[I,W]
291.89 Alcohol-Induced Anxiety Disorder[I,W]
291.89 Alcohol-Induced Sexual Dysfunction[I]
291.89 Alcohol-Induced Sleep Disorder[I,W]
291.9 Alcohol-Related Disorder NOS

AMPHETAMINE (OR AMPHETAMINE-LIKE)–RELATED DISORDERS

Amphetamine Use Disorders
304.40 Amphetamine Dependence[a,b,c]
305.70 Amphetamine Abuse

Amphetamine-Induced Disorders
292.89 Amphetamine Intoxication
Specify if: With Perceptual Disturbances
292.0 Amphetamine Withdrawal
292.81 Amphetamine Intoxication Delirium
292.xx Amphetamine-Induced Psychotic Disorder
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Amphetamine-Induced Mood Disorder[I,W]
292.89 Amphetamine-Induced Anxiety Disorder[I]
292.89 Amphetamine-Induced Sexual Dysfunction[I]
292.89 Amphetamine-Induced Sleep Disorder[I,W]
292.9 Amphetamine-Related Disorder NOS

CAFFEINE-RELATED DISORDERS

Caffeine-Induced Disorders
305.90 Caffeine Intoxication
292.89 Caffeine-Induced Anxiety Disorder[I]
292.89 Caffeine-Induced Sleep Disorder[I]
292.9 Caffeine-Related Disorder NOS

CANNABIS-RELATED DISORDERS

Cannabis Use Disorders
304.30 Cannabis Dependence[a,b,c]
305.20 Cannabis Abuse

Cannabis-Induced Disorders
292.89 Cannabis Intoxication
Specify if: With Perceptual Disturbances
292.81 Cannabis Intoxication Delirium
292.xx Cannabis-Induced Psychotic Disorder
.11 With Delusions[I]
.12 With Hallucinations[I]
292.89 Cannabis-Induced Anxiety Disorder[I]
292.9 Cannabis-Related Disorder NOS

COCAINE-RELATED DISORDERS

Cocaine Use Disorders
304.20 Cocaine Dependence[a,b,c]
305.60 Cocaine Abuse

Cocaine-Induced Disorders
292.89 Cocaine Intoxication
Specify if: With Perceptual Disturbances
292.0 Cocaine Withdrawal
292.81 Cocaine Intoxication Delirium
292.xx Cocaine-Induced Psychotic Disorder
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Cocaine-Induced Mood Disorder[I,W]
292.89 Cocaine-Induced Anxiety Disorder[I,W]
292.89 Cocaine-Induced Sexual Dysfunction[I]
292.89 Cocaine-Induced Sleep Disorder[I,W]
292.9 Cocaine-Related Disorder NOS

HALLUCINOGEN-RELATED DISORDERS

Hallucinogen Use Disorders
304.50 Hallucinogen Dependence[b,c]
305.30 Hallucinogen Abuse

Hallucinogen-Induced Disorders
292.89 Hallucinogen Intoxication
292.89 Hallucinogen Persisting Perception Disorder (Flashbacks)
292.81 Hallucinogen Intoxication Delirium
292.xx Hallucinogen-Induced Psychotic Disorder
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Hallucinogen-Induced Mood Disorder[I]
292.89 Hallucinogen-Induced Anxiety Disorder[I]
292.9 Hallucinogen-Related Disorder NOS

INHALANT-RELATED DISORDERS

Inhalant Use Disorders
304.60 Inhalant Dependence[b,c]
305.90 Inhalant Abuse

Inhalant-Induced Disorders
292.89 Inhalant Intoxication
292.81 Inhalant Intoxication Delirium
292.82 Inhalant-Induced Persisting Dementia
292.xx Inhalant-Induced Psychotic Disorder
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Inhalant-Induced Mood Disorder[I]
292.89 Inhalant-Induced Anxiety Disorder[I]
292.9 Inhalant-Related Disorder NOS

NICOTINE-RELATED DISORDERS

Nicotine Use Disorder
305.1 Nicotine Dependence[a,b]

Nicotine-Induced Disorder
292.0 Nicotine Withdrawal
292.9 Nicotine-Related Disorder NOS

TABLE 3–1. DSM-IV-TR classification of delirium, dementia, and amnestic and other cognitive disorders; mental disorders due to a general medical condition not elsewhere classified; and substance-related disorders *(continued)*

Substance-Related Disorders *(continued)*

OPIOID-RELATED DISORDERS

Opioid Use Disorders
304.00 Opioid Dependence[a,b,c,d]
305.50 Opioid Abuse

Opioid-Induced Disorders
292.89 Opioid Intoxication
Specify if: With Perceptual Disturbances
292.0 Opioid Withdrawal
292.81 Opioid Intoxication Delirium
292.xx Opioid-Induced Psychotic Disorder
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Opioid-Induced Mood Disorder[I]
292.89 Opioid-Induced Sexual Dysfunction[I]
292.89 Opioid-Induced Sleep Disorder[I,W]
292.9 Opioid-Related Disorder NOS

PHENCYCLIDINE (OR PHENCYCLIDINE-LIKE)–RELATED DISORDERS

Phencyclidine Use Disorders
304.60 Phencyclidine Dependence[b,c]
305.90 Phencyclidine Abuse

Phencyclidine-Induced Disorders
292.89 Phencyclidine Intoxication
Specify if: With Perceptual Disturbances
292.81 Phencyclidine Intoxication Delirium
292.xx Phencyclidine-Induced Psychotic Disorder
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Phencyclidine-Induced Mood Disorder[I]
292.89 Phencyclidine-Induced Anxiety Disorder[I]
292.9 Phencyclidine-Related Disorder NOS

SEDATIVE-, HYPNOTIC-, OR ANXIOLYTIC-RELATED DISORDERS

Sedative, Hypnotic, or Anxiolytic Use Disorders
304.10 Sedative, Hypnotic, or Anxiolytic Dependence[a,b,c]
305.40 Sedative, Hypnotic, or Anxiolytic Abuse

Sedative-, Hypnotic-, or Anxiolytic-Induced Disorders
292.89 Sedative, Hypnotic, or Anxiolytic Intoxication
292.0 Sedative, Hypnotic, or Anxiolytic Withdrawal
Specify if: With Perceptual Disturbances
292.81 Sedative, Hypnotic, or Anxiolytic Intoxication Delirium
292.81 Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium
292.82 Sedative-, Hypnotic-, or Anxiolytic-Induced Persisting Dementia
292.83 Sedative-, Hypnotic-, or Anxiolytic-Induced Persisting Amnestic Disorder

SEDATIVE-, HYPNOTIC-, OR ANXIOLYTIC-RELATED DISORDERS *(continued)*

Sedative-, Hypnotic-, or Anxiolytic-Induced Disorders *(continued)*
292.xx Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder
.11 With Delusions[I,W]
.12 With Hallucinations[I,W]
292.84 Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder[I,W]
292.89 Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder[W]
292.89 Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction[I]
292.89 Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder[I,W]
292.9 Sedative-, Hypnotic-, or Anxiolytic-Related Disorder NOS

POLYSUBSTANCE-RELATED DISORDER
304.80 Polysubstance Dependence[a,b,c,d]

OTHER (OR UNKNOWN) SUBSTANCE–RELATED DISORDERS

Other (or Unknown) Substance Use Disorders
304.90 Other (or Unknown) Substance Dependence[a,b,c,d]
305.90 Other (or Unknown) Substance Abuse

Other (or Unknown) Substance–Induced Disorders
292.89 Other (or Unknown) Substance Intoxication
Specify if: With Perceptual Disturbances
292.0 Other (or Unknown) Substance Withdrawal
Specify if: With Perceptual Disturbances
292.81 Other (or Unknown) Substance–Induced Delirium
292.82 Other (or Unknown) Substance–Induced Persisting Dementia
292.83 Other (or Unknown) Substance–Induced Persisting Amnestic Disorder
292.xx Other (or Unknown) Substance–Induced Psychotic Disorder
.11 With Delusions[I,W]
.12 With Hallucinations[I,W]
292.84 Other (or Unknown) Substance–Induced Mood Disorder[I,W]
292.89 Other (or Unknown) Substance–Induced Anxiety Disorder[I,W]
292.89 Other (or Unknown) Substance–Induced Sexual Dysfunction[I]
292.89 Other (or Unknown) Substance–Induced Sleep Disorder[I,W]
292.9 Other (or Unknown) Substance–Related Disorder NOS

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Although many persons are less aware of their memory difficulty than are other observers (Frerichs and Tuokko 2006), older adults often complain of memory difficulties: 83% report forgetting names frequently, 60% report losing objects such as keys, and 57% report forgetting telephone numbers that were just checked (Bolla et al. 1991). Although older adults recall as well as younger adults the gist of material they have learned, they recall details less well (Ulatowska et al. 1998). Because they rely on their general world knowledge to supplement their memory, older adults are also more prone to errors in recall.

The current conceptualization of memory includes conscious and unconscious memory (see Figure 3–1). Conscious (explicit, declarative) memory includes recall of people, places, objects, facts, and events. It includes semantic memory, working memory, and episodic memory. Semantic memory deals with facts, such as the color of an orange, learned over periods of time ranging from minutes to years; working memory is the ability to manipulate over a period of seconds to minutes information that may not be stored, such as retaining a new telephone number before dialing; and episodic memory deals with time-associated memories stored for minutes to years (e.g., what a person did yesterday). Unconscious (implicit, procedural) memory deals with sequences of events involving the motor system (e.g., skills such as riding a bicycle) that do not require conscious recall. It also includes classical conditioning, habits, habituation (desensitization), and priming (the increased ability to recognize stimuli based on recent experience with them). Through rehearsal, conscious memory of the steps in performing complex tasks can become unconscious.

The various memory functions appear to involve different mechanisms and different brain circuitry (reviewed in Budson and Price 2005). Short-term memory is achieved by neurotransmitter-induced long-term potentiation that strengthens synaptic connections. It can be disrupted by blocking the action of acetylcholine. Long-term storage of memories involves the outgrowth of new axon terminals and the development of new synapses. This can be blocked by protein synthesis inhibitors. The prefrontal cortex appears to be the site of working memory. The hippocampus transfers memory from short-term to long-term storage, and the portions of the cortex that originally processed the information are the sites of long-term storage of explicit memory (Squire 1992). The corpus striatum and cerebellum form part of the circuitry for procedural memory (Wenk 1999).

There is little change in working memory with aging (Drachman and Leavitt 1972). Encoding and retrieval from episodic memory appear to decline with normal aging, especially when the information cannot be placed in context (Schludermann et al. 1983), but vocabulary, general information, and recall of past historical or personal events remain relatively intact (Poon 1985). A cross-sectional study of cognitively normal individuals ranging from age 62 to 100 years showed that learning ability decreased with advancing age (unrelated to education), but recall, adjusted for the amount of material initially learned, did not (Petersen et al. 1992). Thus, healthy older adults' memory is generally preserved for relevant, well-learned material, but their ability to process novel information declines. Slowing the presentation of new information helps normal older adults; cuing helps them retrieve more effectively from recent memory (Derouesne and Lacomblez 2000). However, memory aids are not very helpful when Alzheimer disease reaches the level of dementia.

Executive Function

Although the most common cognitive complaint of elders is impaired recall of names and recent events, the cognitive decline associated with normal aging occurs largely in executive function and is thought to be related primarily to loss of synapses in the prefrontal cortex and loss of dopaminergic input to the prefrontal cortex from the corpus striatum. This decline manifests as failure to suppress interfering information, making of perseverative errors, and inability to organize working memory. Loss of dopaminergic function in the caudate nucleus and the putamen, through reduction of dopamine D_2 and D_3 receptors and dopamine transporter, accounts for almost all of the variance in recognition and working memory tasks between younger and older adults (reviewed in Hedden and Gabrieli 2005). Older adults examined with functional magnetic resonance imaging techniques during cognitive tasks show bilateral prefrontal cortical activation. In contrast, younger persons show only unilateral activation, suggesting elders' compensatory need to recruit more neuronal circuits (Persson et al. 2004).

Mild Cognitive Impairment

The proposed syndrome of age-associated memory impairment (Crook et al. 1986) has been largely supplanted by the designation of *mild cognitive impairment* (MCI; Petersen et al. 1997), a term that does not appear in DSM-IV-TR. The effort to identify individuals at high risk for developing Alzheimer disease or other dementing illness is discussed at greater length in Chapter 9, "Mild Cognitive Impairment."

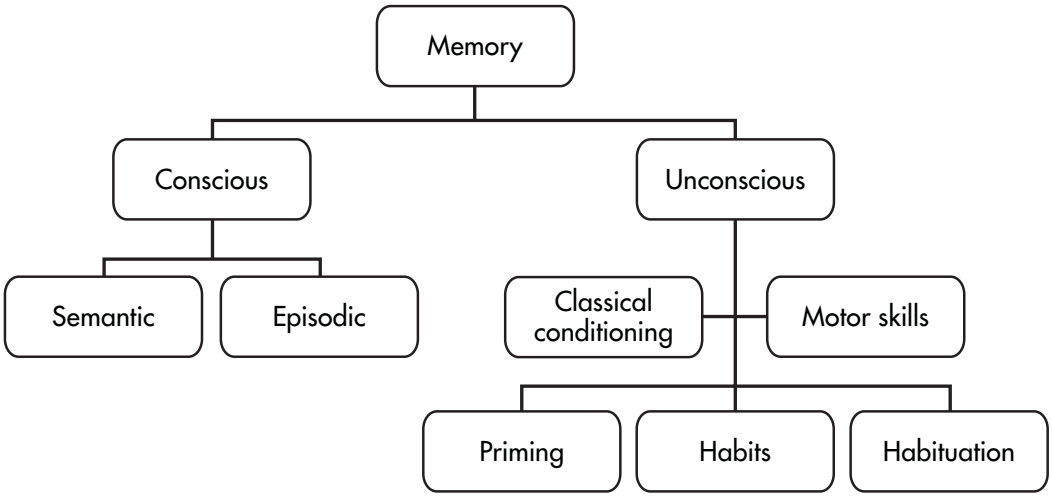

FIGURE 3–1. Structure of memory.

Individuals with MCI have complaints of poor memory, normal activities of daily living and general cognitive function, and abnormal memory function for their age, and they do not meet criteria for dementia (Petersen et al. 1999). For the purpose of therapeutic trials, criteria for MCI include 1) a history of insidiously developing memory impairment and 2) documentation of impaired memory by a delayed recall score 1.5–2 standard deviations below an age-adjusted norm on the Logical Memory subtest of the Wechsler Memory Scale, a Clinical Dementia Rating Scale score of 0.5, and a Mini-Mental State Examination score of 24–30 (Petersen et al. 2005). Many persons with MCI would be diagnosed by some clinicians as having early Alzheimer disease. Indeed, a postmortem study of 15 persons with MCI diagnosed by Petersen and colleagues' criteria showed that all had pathological findings involving medial temporal lobe structures suggestive of evolving Alzheimer disease (Petersen et al. 2006).

MCI has been divided into subtypes, including purely amnestic, amnestic plus other cognitive domains (e.g., attention, visuospatial function, language, executive function), and single- or multiple-domain nonamnestic MCI. Those at greatest risk for conversion to Alzheimer disease appear to have severe memory impairment plus impairment in one or more other cognitive domains, whereas single- or multiple-domain nonamnestic subtypes are more likely to convert to other dementias (Tabert et al. 2006). Functional imaging has also been used to predict conversion from amnestic MCI to Alzheimer disease. Positron emission tomography of 30 subjects with MCI had 92% sensitivity and 89% specificity for detecting subjects who progressed to a diagnosis of Alzheimer disease after a mean follow-up interval of 18 months (Drzezga et al. 2005). In the same study, the apolipoprotein E ε4 genotype was found to have only 75% sensitivity and 56% specificity.

Winblad et al. (2004) suggested expanding the criteria for MCI as follows: 1) the person is neither normal nor demented; 2) the person's cognitive deterioration is shown by objective measurements over time, or the patient's and/or informant's subjective report of decline is accompanied by objective cognitive deficits; and 3) the person's activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. There is insufficient information to know the relationship between this more broadly defined MCI and the eventual development of dementing illness. In a large cohort study (N=2,220), high numbers of depressive symptoms at baseline, as well as vascular disease measures, were associated over 6 years with greater progression to this more broadly defined MCI (Barnes et al. 2006).

In our experience, the most sensitive clinical tests for incipient Alzheimer disease include impaired concentration, impaired recent memory (difficulty recalling three or four words after a brief distraction), and impaired remote memory. Assessment of remote memory is confounded by education when using general knowledge questions such as names of past U.S. presidents or historical events. Remote memory is more effectively tested by gathering from knowledgeable informants specific patient-relevant information, such as family events or the number, names, and ages of grandchildren. Another sensitive indicator is loss of the abstract attitude, as demonstrated by performance in recognizing similarities and interpreting proverbs. However, proverb interpretation is highly culture bound and may yield false-positive results for persons from other cultures. Performance on recognizing similarities, although not culture bound, is related strongly to education and pre-

morbid intelligence. Early in the course of Alzheimer disease, patients may also demonstrate impaired verbal fluency (e.g., in trying to name all the animals they can think of in 1 minute), dysnomia (difficulty with object naming), constructional dyspraxia (difficulty drawing simple geometric figures; see Appendix C), and executive dysfunction (e.g., difficulty drawing the face of a clock and setting the time). There are no clinical criteria for diagnosis of prodromal non-Alzheimer disease cognitive disorders.

Dementia

Dementia is an impairment of multiple cognitive abilities, including memory, that is sufficient to interfere with self-maintenance, work, and social relationships. The diagnosis is based on the clinical history (usually supplied by informants other than the patient) and mental status examination. At times, the history and clinical examination will suggest the etiology of the dementia, as in the case of a person who has experienced multiple strokes. At other times, extensive interdisciplinary evaluation and laboratory procedures (radiological, biochemical, genetic, and/or psychological tests) are required to determine the cause of dementia.

The diagnosis of dementia is complicated by the enormous variation across individuals. Many persons who have declined cognitively may still function at a level comparable to that of an average person of the same age. Therefore, the clinician must compare a person's present abilities with the patient's own past abilities. This can usually be accomplished by the retrospective accounts furnished by patients or their families. However, family members' accounts are subject to bias (Davis et al. 2006). Family members often minimize deficits by stating that a loved one who appears impaired on clinical examination was never good with numbers or interested in reading or current events. Individual family members' biases are minimized through the use of multiple informants. Also, more accurate data can be obtained through the use of simple tools such as the History Form (see Appendix A) and the Level of Function Scale (see Appendix B), which we use in our clinic.

The DSM-IV-TR criteria for dementia listed in Table 3–2 include the clinical means to elicit the diagnostic signs and symptoms. Table 3–3 indicates the criteria for diagnosing specific dementias. The DSM-IV-TR description of dementia does not imply either continued progression or irreversibility.

Minor degrees of cognitive impairment, especially due to medications or metabolic disorders, are frequently reversible, but a full-blown dementia syndrome is rarely reversible. In a review of 32 studies of elderly patients with cognitive impairments, Clairfield (1988) found that potentially reversible causes of dementia accounted for 13.2% of the cases. In the 11 studies that provided follow-up, 8% of the cases of dementia resolved partially, and only 3% resolved fully. Reversible causes of dementia included drug use (28%), depression (26%), and toxic-metabolic problems (15.5%).

According to a report in 1992, *treatable* causes of dementia accounted for about 10.5% of cases and included neurosyphilis, fungal infections, tumor, alcohol abuse, subdural hematoma, normal-pressure hydrocephalus, and epilepsy (Katzman 1992). Our present-day ability to treat Alzheimer disease and vascular dementia brings the percentage of treatable conditions to more than 70%. *Reversible* dementias, including those caused by drug toxicity, metabolic disorders, hyponatremia, vitamin B_{12} deficiency, hypothyroidism, and hypoglycemia, still account for only 4.7% of cases (Katzman 1992).

Delirium

Delirium is a state of altered consciousness and cognition, usually of acute onset (hours or days) and of brief duration (days or weeks). The hallmark of delirium is impaired attention. Many persons may remain oriented to person, place, and time but demonstrate impairments on tests of sustained attention, such as digit span and naming months of the year in reverse. Sleep-wake disturbances are common, as are reduced or increased psychomotor activity. Hallucinations are also frequent. In a series of 227 patients with DSM-IV-TR delirium, 27% experienced visual hallucinations, 12.4% auditory hallucinations, and 2.7% tactile hallucinations (Webster and Holroyd 2000). Delirium is usually characterized by generalized slow waves in the electroencephalogram (EEG); the course of delirium can be followed with serial EEGs (Engel and Romano 1959). The DSM-IV-TR criteria for delirium due to a general medical condition are presented in Table 3–4.

Delirium is very common in general hospital patients. Estimates of prevalence before 1990 ranged from 30% to 50% in persons age 70 years or older (Lipowski 1987). In a more recent prospective study of 225 nonconfused individuals age 65 years or older who were undergoing repair of hip fracture or elective hip replacement surgery, DSM-IV-TR delirium was diagnosed in 20%. The incidence was 24% in the group with hip fractures and only 12% in those undergoing elective hip replacement; the former group probably had greater baseline cognitive impairment

TABLE 3–2. General diagnostic criteria for dementia based on DSM-IV-TR criteria

A. The development of multiple cognitive deficits manifested by both

(1) memory impairment (impaired ability to learn new information and to recall previously learned information)

(a) Working memory can be assessed by digit span forward and in reverse, with a discrepancy of three digits or more suggesting impairment. Short-term memory can be tested by asking the examinee to recall three words presented by the examiner after an interval of 5 minutes. Short-term memory can also be tested by presenting three objects without naming them, covering them up, and asking the examinee to name them 5 minutes later. Another test of short-term memory is to read a short paragraph aloud to the examinee and then ask the examinee to tell what he or she recalls.

(b) Long-term memory is tested by asking the examinee for personal information that can be validated by the accompanying person (date of birth, graduation from high school, marriage, etc.) and by asking facts of common knowledge compatible with the examinee's education and cultural background, including questions such as the name of the president of the United States, the immediate past presidents, the state capital, or the location of the U.S. Capitol.

(2) one (or more) of the following cognitive disturbances:

(a) aphasia (language disturbance), including, in addition to the classic aphasias, difficulty with word finding and confrontational naming. Word finding difficulty is evidenced in advanced dementia by empty speech devoid of nouns and verbs, with relative preservation of socially overlearned speech, such as "How are you?" Earlier, it can be demonstrated by asking the subject to name as many animals as possible in 1 minute. Patients with Alzheimer disease will typically name fewer than 10 animals and will often repeat names. They also have difficulty naming the parts of a watch (watchband, stem, back, crystal), making paraphasic errors (e.g., *strap* for band or *lens* for crystal) or describing functions (e.g., "It's how you set it" for watch stem) instead.

(b) apraxia (inability to carry out motor activities despite intact motor function, e.g., strength and coordination). This difficulty is demonstrated when the examinee is asked, for example, to demonstrate how to turn a key in a lock.

(c) agnosia (failure to recognize or identify objects despite intact sensory function).

(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting).

1. Impaired planning, organizing, and sequencing are indicated by an examinee's inability to deal with interpersonal, family, and employment-related issues and to describe logically how they might be dealt with. Changes in long-standing habits and personal hygiene may reflect executive dysfunction. The best source of information about executive functioning may be the examinee's history, but executive functioning may also be evaluated by asking the examinee how to deal with problems that individuals might encounter in daily life, such as an overdrawn bank account or a medical emergency. Executive functioning can also be assessed by asking examinees to perform serial tasks, such as going through the steps of mailing a letter (i.e., folding the paper, inserting it into an envelope, addressing the envelope, placing a stamp on it, and sealing it).
2. Impaired abstracting ability is evidenced by the examinee's inability to abstractly categorize the similarity between objects such as a chair and a table, or a knife and a fork, or for highly educated persons, between a poem and a statue, or praise and punishment. Impaired abstracting ability is also evidenced by the examinee's inability to abstractly interpret common proverbs. [See Appendix C for detailed mental status examination.]

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The deficits do not occur exclusively during the course of delirium.

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TABLE 3–3. DSM-IV-TR diagnostic criteria for specific dementia syndromes

Diagnostic criteria for dementia of the Alzheimer's type

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., major depressive disorder, schizophrenia).

Diagnostic criteria for vascular dementia

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not occur exclusively during the course of a delirium.

Diagnostic criteria for dementia due to other general medical conditions

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

TABLE 3–3. DSM-IV-TR diagnostic criteria for specific dementia syndromes *(continued)*

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition other than Alzheimer's disease or cerebrovascular disease (e.g., HIV infection, traumatic brain injury, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, normal-pressure hydrocephalus, hypothyroidism, brain tumor, or vitamin B_{12} deficiency).

D. The deficits do not occur exclusively during the course of a delirium.

Diagnostic criteria for substance-induced persisting dementia

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The deficits do not occur exclusively during the course of a delirium and persist beyond the usual duration of substance intoxication or withdrawal.

D. There is evidence from the history, physical examination, or laboratory findings that the deficits are etiologically related to the persisting effects of substance use (e.g., a drug of abuse, a medication).

Diagnostic criteria for dementia due to multiple etiologies

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance has more than one etiology (e.g., head trauma plus chronic alcohol use, dementia of the Alzheimer's type with the subsequent development of vascular dementia).

D. The deficits do not occur exclusively during the course of a delirium.

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(Duppils and Wikblad 2000). The onset of delirium was postoperative in 96% of patients and generally resolved within 48 hours. Predisposing factors were older age, cognitive impairment, and preexisting brain disease. A 20% point prevalence of delirium in persons age 70 years or older was found in 250 consecutive admissions to an acute medical unit of an inner-city teaching hospital in the United Kingdom (Tabet et al. 2005). It seems likely that the prevalence of delirium in hospitalized elders has actually reduced over the past 20 years, due possibly to shorter lengths of stay, less invasive diagnostic and treatment procedures, and greater staff sophistication. Outpatient surgery undoubtedly reduces the prevalence of delirium as well.

TABLE 3–4. DSM-IV-TR diagnostic criteria for delirium due to a general medical condition

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

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A major risk factor for delirium is underlying cognitive dysfunction. In many individuals, the first sign of a cognitive disorder is postoperative delirium. In our experience, episodes of delirium frequently point to the impending development of dementia with Lewy bodies. Delirium has a greater degree of personality disorganization and clouding of consciousness than does dementia. Fluctuating cognitive ability occurs in dementia but not to the extent or with the rapidity (minutes or hours) that it occurs in delirium. Dementia patients usually give their best cognitive performance early in the day when they are not fatigued, under circumstances in which they do not feel challenged or anxious. Toward the end of the day, many cognitively impaired persons become transiently delirious, a phenomenon often referred to as *sundowning*. Although sundowning is often attributed to the waning of sensory cues, Volicer et al. (2001) suggested that in Alzheimer disease, the mechanism of sundowning may be a disturbance of circadian rhythm related to a phase delay in body temperature.

Delirium may also be caused by psychotropic drugs administered to alleviate behavioral symptoms in dementia patients (Lim et al. 2006) or by nonpsychotropic drugs with strong anticholinergic effects (Womack and Heilman 2003). The diagnosis of dementia cannot be made in the presence of delirium; the patient must be clear of the acute disturbance.

The following two cases of delirium (courtesy of Kip Queen, M.D.) were seen in a general hospital by a psychiatric consultation service.

Case 1

A 66-year-old woman with a past history of seizures was brought by police to a hospital after she called 911 repeatedly to report burglars in her home. She had apparently fallen and then become agitated. She had also become combative with her male housemate and had threatened him with a knife. This was an acute change in her mental status. At the hospital, she was agitated, moving around and talking continuously. She was alert and oriented to person, time, and place, but she had difficulty maintaining adequate attention to perform simple cognitive tasks. She was guarded and suspicious with staff. She was not depressed, but her emotional responses were restricted. She had delusions concerning burglars in her home and had mistaken her companion for a burglar.

Her family reported no past psychiatric history, but on reflection, they reported that there might have been some decline in functioning and cognition over the previous year. Although she was reported to have a seizure disorder, she was on no medications and had had no recent seizures. Her past medical history included a hysterectomy and refractive eye surgery. Her only drug allergy was codeine.

She had three children. She did not use drugs or alcohol. She had worked in the past as a medical assistant and most recently as a parking attendant; she had retired 4 months previously. Her male companion was wheelchair bound.

On physical examination, she was cachectic and appeared ill. Her vital signs were normal; her gait was ataxic and unstable. A computed tomographic scan of the head showed soft tissue swelling on the right side of her head but no intracranial pathology. A chest X ray was normal. Complete blood count and blood chemistries (including cardiac enzymes) were normal, as was examination of her cerebrospinal fluid. Thyroid hormone, vitamin B_{12}, and folic acid levels were normal. A serological test for syphilis was negative. Urinalysis revealed a large amount of protein and ketone bodies, nitrites, and numerous bacteria.

In hospital, she remained delirious, with confusion, hallucinations, and suspiciousness of staff, and she had a hypotensive episode that was attributed to volume depletion. She was treated with low-dose antipsychotic agents for agitation and was started empirically on ciprofloxacin for her urinary tract infection. After 5 days in the hospital, she improved to the point that she could be discharged to her own care. It was thought that she had experienced an acute delirium from a urinary tract infection superimposed on early Alzheimer disease.

Case 2

A 73-year-old man was brought to a psychiatric emergency facility by police after they received a 911 call from his wife, whom he had held down by force and threatened with a shotgun, believing her to be a burglar. His wife dated his change in mental status to a month previously, when he was hospitalized following a seizure. He had developed a seizure disorder 10 years earlier, following surgical evacuation of a brain abscess, but

had been seizure free on diphenylhydantoin for many years. He began having periods of confusion and irritability after his recent discharge from the hospital; these worsened after he was started on quetiapine and levetiracetam a week previously.

His family reported a history of memory problems since his brain surgery. He had been independent in activities of daily living until his recent seizure, but his wife had been helping him with their finances since his brain surgery. In the previous 6 months, his cognition had declined. He needed his wife to help navigate while driving and was no longer keeping up with current events or hobbies.

Aside from a craniotomy for evacuation of a brain abscess and hypertension, he had no significant medical history.

This man was married, and had four children. He had been a truck driver prior to his brain abscess; he had been retired since then. He did not use drugs or alcohol.

Laboratory studies were unremarkable aside from magnetic resonance imaging evidence of encephalomalacia of the right parieto-occipital lobe, a left caudate infarct, and a left posterior cerebral artery watershed infarction.

On examination, he had problems with naming, comprehension, and repetition. His initial score on the Mini-Mental State Examination was 8; he was unable to draw a clock. He was very confused when admitted to the hospital, had visual hallucinations, and made numerous attempts to pull out his intravenous lines. He improved significantly within 24–48 hours after discontinuation of levetiracetam. He was thought to have had a mild dementia due to his brain injury and several inobvious strokes with a superimposed delirium due to levetiracetam. At discharge, he was alert, oriented to person and place, and no longer hallucinating.

Amnestic Disorder

The primary manifestation of amnestic disorder is memory impairment. The DSM-IV-TR diagnostic criteria for this uncommon disorder are presented in Table 3–5. When part of a dementia syndrome, amnestic disorder is not diagnosed separately. The most common cause of persisting amnestic disorder is thiamine deficiency, which is typically associated with malnutrition accompanying long-term alcohol dependence and is often preceded by the delirium, ophthalmoplegia, and ataxia of Wernicke encephalopathy. The symptoms of Korsakoff syndrome (or substance-induced persisting amnestic disorder due to alcohol, per DSM-IV-TR) differ from those of Alzheimer disease. In the former, an individual may recall rules and principles for organizing information and have access to previously acquired knowledge with impairment of recent memory; in the latter, the person may have little access to previously acquired information, with resultant difficulty in encoding ongoing events (Weingartner et al. 1983).

TABLE 3–5. DSM-IV-TR diagnostic criteria for amnestic disorder due to a general medical condition

A. The development of memory impairment as manifested by impairment in the ability to learn new information or the inability to recall previously learned information.

B. The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.

C. The memory disturbance does not occur exclusively during the course of a delirium or a dementia.

D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition (including physical trauma).

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Persistent amnesia may result from many types of brain injury. The best known cause, bilateral hippocampal lesions, impairs recent memory and prevents additional storage but does not impair memories that were stored before the injury (Scoville and Milner 1957; Zola-Morgan et al. 1986).

Amnestic episodes occur with the short-acting benzodiazepines such as lorazepam and triazolam. These episodes are usually transient but may confound diagnosis of dementia or amnestic disorder. The importance of considering amnestic disorders in differential diagnosis is that they are reversible when due to drugs and partly reversible in Wernicke encephalopathy.

Other Cognitive Disorders

According to DSM-IV-TR, cognitive disorder not otherwise specified indicates cognitive dysfunction presumed to be due to the direct effect of a general medical condition. It does not meet criteria for delirium, dementia, or amnestic disorder. Examples include impairment in cognitive functioning on neuropsychological testing or quan-

tified clinical assessment, accompanied by objective evidence of a systemic illness or central nervous system dysfunction. A common example is postconcussion disorder, with impaired memory or attention following head trauma. Another common example is postoperative cognitive dysfunction (POCD).

Older adults often complain of deficits in cognitive function following major noncardiac surgery. In a prospective study measuring memory, attention, cognitive speed, and speed of general information processing, deficits were present at 1 week after surgery but largely gone 3 months later. However, 6 months after surgery, 29% of patients continued to complain of cognitive deficits (Dijkstra et al. 1999). A prospective study of POCD in 1,218 persons age 60 or older undergoing major noncardiac surgery under general anesthesia showed cognitive dysfunction in 26% of patients at 1 week after surgery and in 10% at 3 months, compared with control rates of 3.4% and 2.8%, respectively, in age-matched persons who had not undergone surgery (Biedler et al. 1999). In this study, risk factors for early POCD were increasing age and duration of anesthesia, little education, a second operation, postoperative infection, and respiratory complications. Only age was a risk factor for long-term POCD. A more recent meta-analysis of controlled surgical studies found no difference in POCD in the immediate postoperative period when general anesthesia versus regional anesthesia was used (Bryson and Wyand 2006). A long-term study comparing individuals who had undergone coronary artery bypass surgery with a control group having known risk factors for coronary artery disease pointed to the need for appropriate control groups in long-term studies of POCD. Using controls with similar risk factors, there was no significant difference in neuropsychological test results at 1 or 3 years following surgery (Selnes et al. 2005).

We now turn our attention to the group of psychiatric disorders that should be considered in the assessment of a person with cognitive complaints or symptoms; the most common is major depression.

Major Depressive Disorder

Depression must be considered in the evaluation of a person with a cognitive complaint or with objective evidence of cognitive impairment, whether as a primary diagnosis or as a complication of an underlying disease (see also Chapter 15 of this volume). Many depressed persons experience cognitive impairment, although the severity of their impairment does not correspond with the severity of their depressive symptoms. Much attention has been paid to the phenomenon of *pseudodementia* (more appropriately termed the *dementia of depression*) (Kiloh 1961).

Cognitive processes impaired by depression are attention, perception, speed of cognitive response, problem solving, memory, and learning. Depressed persons appear to use weak or incomplete strategies to encode events to be remembered. With provision of organization and structure, memory deficits tend to disappear (Weingartner et al. 1981). The cognitive and motor tasks that are most impaired are those requiring sustained effort (Cohen et al. 1982). Although Sternberg and Jarvik (1976) reported that patients' short-term memory deficits are correctable by successful treatment with antidepressants and Greenwald et al. (1989) found that patients' Mini-Mental State Examination scores improved after successful treatment, more recent studies suggest that persistent deficits in cognitive function, including working memory, speed of information processing, episodic memory, and attention, follow remission of depressive symptoms (Nebes et al. 2003). Age differences may play a role in the type of cognitive symptoms affected by depression. In one study, elderly depressed persons performed more poorly than younger depressed persons on tests of executive function but not on tests of selective or sustained attention (Lockwood et al. 2002).

The response of both depressive and cognitive symptoms to antidepressant treatment does not firmly establish elderly patients' sole diagnosis as depression. Of 23 elderly patients who had amelioration of cognitive symptoms with treatment of their depression, nearly half later developed a dementing illness (Alexopoulos et al. 1993).

The extent to which depression occurs comorbidly with Alzheimer disease is highly controversial, in part due to the substantial overlap of depressive symptoms with the symptoms of Alzheimer disease. Most of the nine DSM-IV-TR criteria for major depression, including decreased interest in activities, weight loss, insomnia or hypersomnia, loss of energy, and diminished ability to think or concentrate, can also be related directly to the effects of Alzheimer disease. The most important diagnostic difficulty arises from the fact that DSM-IV-TR does not require depressed mood in the diagnosis of major depression. Lyketsos and Olin (2002) reported 50% prevalence of depressive disorders in Alzheimer disease. In a multicenter study employing the same diagnostic criteria across centers, the incidence of major depression in Alzheimer disease patients ranged from 22.5% to 54.4% (Zubenko et al. 2003). Weiner and Sairam (2000) proposed to reduce diagnostic confusion between major depression and Alzheimer disease by requiring that five or more of the following nine criteria be present for at least

1 week and nearly every day: sadness most of the day, no apparent enjoyment when engaged by others in ordinarily pleasurable activities (or active refusal to be engaged), little interest in food when presented by others and helped to engage in eating, increased irritability, psychomotor agitation or retardation, low energy, feelings of worthlessness or crying, function below expectation for the level of cognitive impairment, and expressions of a positive wish to die and suicide plans or attempts. Olin et al. (2002) suggested similar criteria.

In our experience, depressive syndromes are a common cause of cognitive impairment in persons without demonstrable brain pathology, but major depression is an uncommon complication of Alzheimer disease (Weiner et al. 2002). By contrast, there is an approximately 20% prevalence of major depression in the first 2 years after stroke (Robinson 2003), and depression is also frequent in Parkinson disease (McDonald et al. 2003).

DSM-IV-TR criteria for a major depressive episode are presented in Table 3–6. The differentiation between the cognitive impairment of depression and that due to degenerative or metabolic brain disorder is based on the following:

1. Onset of depressive symptoms preceding cognitive impairment
2. Sudden, fairly recent (weeks or months), and often identifiable onset of cognitive impairment, in terms of both time and emotionally important life events (loss of job or spouse)
3. Depressed patient's emphasizing inability to think, concentrate, and remember
4. Signs and symptoms of depression
5. Objective cognitive testing showing depressed patient's deficits to be less severe than his or her complaints, with performance improved by encouragement, cuing, and structure
6. Depressed patients more commonly giving "I don't know" answers in contrast to making near misses, confabulating, or repeating (perseverating) answers
7. Normal EEG
8. Absence of any condition known to affect brain function

Neither radiological evidence of mild generalized brain atrophy in elderly persons nor a positive dexamethasone suppression test is useful in differentiating depression from a dementing illness. As indicated in Chapter 5, "Neuropsychological Assessment in Dementia," neuropsychological testing can help distinguish depression from degenerative or metabolic brain disorder and can also identify depression in persons with cognitive impairment.

Bipolar Disorder

The depressive phase of bipolar disorder should be clinically evaluated as described above for major depressive disorder. The manic phase is not usually confused with cognitive disorders, but persons with frontotemporal dementias are often confused with manic patients because of their impulsivity, disinhibition, and poor judgment.

Mood Disorder Due to a General Medical Condition

Mood disorder due to a general medical condition and substance-induced mood disorder can be confused with dementia because many of the signs overlap. The essential feature of this disorder is prominent and persistent mood alteration associated with a general medical condition. Carcinoma of the pancreas (Carney et al. 2003), viral illness including hepatitis C (Angelino and Treisman 2006), and stroke (Spalletta et al. 2006) can cause depression. Hyper- or hypothyroidism and hyper- or hypoadrenocorticism can cause depression or mania. The DSM-IV-TR criteria for mood disorder due to a general medical condition are listed in Table 3–7. This disorder usually remits when the underlying cause is treated.

Substance-Induced Mood Disorder

Substance-induced mood disorder is characterized by prominent and persistent mood alteration associated with substance use. Depressive symptoms may be caused by drugs, including reserpine, methyldopa, beta-blockers, interferon (Reichenberg et al. 2005), and some hallucinogens. Exogenous steroids can cause depression or mania. Depressive symptoms usually remit when the causative agent is withdrawn. The DSM-IV-TR criteria for substance-induced mood disorder are listed in Table 3–8.

TABLE 3–6. DSM-IV-TR diagnostic criteria for major depressive episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

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Anxiety Disorder Due to a General Medical Condition

Generalized anxiety or recurrent panic attacks are the chief characteristics of anxiety disorders due to a general medical condition. Endocrine disorders such as hyper- and hypothyroidism, pheochromocytoma, hypercortisolism, and fasting hypoglycemia are potential causative factors, along with a host of others. DSM-IV-TR criteria for anxiety disorder due to a general medical condition are listed in Table 3–9.

Many persons with dementia become distressed or anxious when challenged. Often, the distress or anxiety is expressed through physical complaints when the individual is emotionally stressed. In Alzheimer disease, dysphoria is most common early in the course of illness. Later on, anxiety and mood disturbances often appear to diminish, perhaps because the person's ability to anticipate real or symbolic danger becomes impaired or because patients' communication ability diminishes.

Schizophrenia

Schizophrenia may be a direct cause of impaired cognition or may coexist with a cognitive disorder. The most severely impaired cognitive domains are verbal memory, executive function, attention, verbal fluency, and motor speed (Keefe

TABLE 3–7. DSM-IV-TR diagnostic criteria for mood disorder due to a general medical condition

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:
   (1) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities
   (2) elevated, expansive, or irritable mood

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (e.g., adjustment disorder with depressed mood in response to the stress of having a general medical condition).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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TABLE 3–8. DSM-IV-TR diagnostic criteria for substance-induced mood disorder

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:
   (1) depressed mood or markedly diminished interest or pleasure in all, or almost all, activities
   (2) elevated, expansive, or irritable mood

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
   (1) the symptoms in Criterion A developed during, or within a month of, substance intoxication or withdrawal
   (2) medication use is etiologically related to the disturbance

C. The disturbance is not better accounted for by a mood disorder that is not substance induced. Evidence that the symptoms are better accounted for by a mood disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced mood disorder (e.g., a history of recurrent major depressive episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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and Eesley 2006). The psychotic symptoms that occur in persons with cognitive disorders tend to differ from the psychotic symptoms of schizophrenia. Persons with cognitive disorders rarely develop organized delusional systems with bizarre content. They often accuse others of stealing or attempting to break into their homes, but the patients are unable to offer explanations. The hallucinations of persons with cognitive disorders tend to be visual, whereas those of patients with schizophrenia are more commonly auditory and tend to be accusatory in nature.

An adequate history from family members or caregivers documenting normal adulthood is usually sufficient to distinguish schizophrenia from a cognitive disorder. Schizophrenia usually begins early in life and remains present through the life span. Hallucinations and delusions are generally prominent in the early and middle course of the illness but frequently lessen later on. Few individuals with schizophrenia are able to maintain employment or normal social relationships in the early and middle years of their lives. Occasionally, a high-functioning

TABLE 3–9. DSM-IV-TR diagnostic criteria for anxiety disorder due to a general medical condition

A. Prominent anxiety, panic attacks, or obsessions or compulsions predominate in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (e.g., adjustment disorder with anxiety in which the stressor is a serious general medical condition).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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TABLE 3–10. DSM-IV-TR diagnostic criteria for psychotic disorder due to a general medical condition

A. Prominent hallucinations or delusions.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder.

D. The disturbance does not occur exclusively during the course of a delirium.

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individual with schizophrenia is undiagnosed until later adulthood. In addition, schizophrenia can emerge in the fourth to sixth decades of life. Considerable evidence suggests that the cognitive deficits of schizophrenia precede the psychotic symptoms and are relatively stable over the course of illness despite the presence or absence of active psychosis (Green 2006). Severe cognitive impairment is common among elderly institutionalized patients with schizophrenia, but the etiology of this impairment is largely unknown (Purohit et al. 1998).

Delusional Disorders

Delusional disorders need to be distinguished from cognitive disorders accompanied by delusions because of differences in their management and outcome. The delusions that characterize delusional disorders are commonly erotomanic, grandiose, jealous, persecutory, or somatic. They are expressed with certainty, and attempts to question them are generally met with anger and increasing mistrust. Delusions of persons with Alzheimer disease are less firmly held, transient, and rarely systematized. Among these delusions is that of the phantom boarder—the unseen person or persons that the cognitively impaired person believes are in the house but whose presence the patient cannot understand. Some delusions in cognitive disorders can be viewed in terms of wishful thinking, such as an elderly woman's belief that her children still live with her and are going to school. Other delusions in cognitive disorders, such as the conviction that neighbors are stealing, seem to be attempts to deal with memory impairment.

Psychotic Disorder Due to a General Medical Condition

The DSM-IV-TR diagnostic criteria for psychotic disorder due to a general medical condition are presented in Table 3–10. The criteria specifically exclude psychosis during delirium. Hallucinations and delusions are the most common symptoms of this disorder. Etiologies vary widely but may include brain tumors, seizure disorders, and inflammatory disorders of the brain (e.g., paraneoplastic syndrome) and meninges.

Personality Change Due to a General Medical Condition

General medical conditions may exaggerate preexisting personality traits or cause a change in personality. Brain tumors, head trauma, multiple sclerosis, frontotemporal degenerative diseases, and strokes are common causes of personality changes. Patients demonstrate many different patterns of personality change, but frequent characteristics

TABLE 3–11. DSM-IV-TR diagnostic criteria for personality change due to a general medical condition

A. A persistent personality disturbance that represents a change from the individual's previous characteristic personality pattern. (In children, the disturbance involves a marked deviation from normal development or a significant change in the child's usual behavior patterns lasting at least 1 year.)

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (including other mental disorders due to a general medical condition).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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include emotional instability, recurrent outbursts of aggression or rage, impaired social judgment, apathy, suspiciousness, and paranoid ideation. These symptoms may also occur as interictal phenomena in temporal lobe epilepsy. The DSM-IV-TR criteria for personality change due to a general medical condition are presented in Table 3–11. Although many such cases do not meet criteria for dementia, their functional deficits may be just as severe, as illustrated in the following case.

Case 3

A 69-year-old man was referred for evaluation by his wife and son because he talked to himself, did "silly things," failed to maintain his personal hygiene, and did not pay his bills on time. The patient was a college graduate who had worked at a military installation until he contracted viral encephalitis at age 44 years. He was comatose for a week and experienced residual weakness and slowness of motion. His personality changed. He became highly emotional and negativistic. At age 66 years, he suffered a right-hemisphere stroke that mildly weakened the left side of his body and impaired his speech for a short time.

On examination, the patient was poorly groomed. His speech and language were normal, but he tended to engage in long diatribes. He laughed at inappropriate times during the interview. He had difficulty with concentration when he performed serial subtraction. His recent and remote memory appeared intact. His construction ability was good. He was able to abstractly categorize the similarity between an egg and a seed but was unable to interpret simple proverbs. He had good knowledge of current events but had difficulty when asked to think of an appropriate course of action for dealing with a medical emergency.

Neuropsychological testing revealed a verbal intelligence quotient (IQ) of 117, a performance IQ of 94, and a full-scale score of 108—a performance surpassing 70% of his age peers. There was great scatter in his verbal intellectual abilities from below average to superior. He had difficulty with tasks requiring attention to verbally presented material. His perceptual motor abilities were much poorer, ranging from mentally defective to average. He had difficulty with sequencing social stimuli and with understanding part-whole relationships. He performed poorly on complex verbal problem solving and had mild to moderate difficulty with short- and long-term verbal memory. Language, communication, and constructional abilities were intact.

Mental Retardation

Mental retardation must be considered in the evaluation of cognitive impairment. Except when there are obvious stigmata of a syndrome ordinarily associated with mental retardation (as in Down syndrome), it may be impossible to distinguish clinically between mental retardation and dementia. The examiner must rely instead on the patient's history by an informant. That history usually includes either academic failure with early dropout from school or graduation from a special education program. Job history usually indicates limited skills and limited comprehension. In many instances, educational history can be deceptive. For example, graduation from an ungraded school, despite requiring 10–12 years, may be the equivalent of only a third- or fourth-grade education. Low level and quality of schooling and low intelligence are associated with a poor fund of information and poor abstract reasoning on mental status examination. The mental status examination can help distinguish developmental disorders from dementing illness; patients with dementing illnesses that do not primarily affect language function tend to show less impairment in vocabulary and fund of information than in other aspects of the mental status examination.

Patients with Down syndrome often experience cognitive decline as they age. Those who live past age 35 years demonstrate the microscopic pathology of Alzheimer disease (reviewed by Mann 1988), but not all become demented. Of 57 patients age 30 years or older with Down syndrome, only 28% showed severe cognitive deteriora-

tion at 5-year follow-up (Oliver et al. 1998). The rate of cognitive impairment increased with patient age and the degree of preexisting cognitive impairment. A modest association between inheritance of the ε4 allele of apolipoprotein E and the development of Alzheimer disease also occurs in these individuals (Deb et al. 2000). For this population, as in all others, the clinician should seek remediable causes of functional decline, such as metabolic abnormalities and psychiatric disorders, and not assume that all functional worsening in these patients is due to Alzheimer disease.

Other Psychiatric Disorders

Ganser Syndrome

Ganser syndrome is subsumed in DSM-IV-TR under the heading of dissociative disorder not otherwise specified. The psychological mechanism is that of conversion disorder, and in fact the syndrome has been termed *conversion pseudodementia* (Hepple 2004). The Ganser syndrome differs from malingering (discussed in the next section) in that the mechanism appears to be unconscious. In this syndrome, ludicrous approximate answers (vorbeireden) or responses are made to simple questions or commands, indicating that the patient clearly understands the questions and provides incorrect responses unconsciously (Goldin and MacDonald 1955). For example, when asked to add 2+2, the patient may say the answer is 5. When asked to point upward, the patient may point down, and then the patient may point up when asked to point down. The Ganser syndrome is frequently accompanied by complaints of auditory and visual hallucinations, circumscribed amnesia, and disorientation. Neuropsychological testing yields highly inconsistent performance (Heron et al. 1991), as is also seen in malingering. Symptoms of Ganser syndrome develop rapidly and usually occur in response to a severe environmental stress, such as facing trial or imprisonment. The symptoms are usually short lived and require essentially no active treatment. Of interest, one element of this syndrome, the deliberate choice of incorrect answers to questions, has been reported in a case of clinically diagnosed frontotemporal dementia (Ladowsky-Brooks and Fischer 2003).

Malingering

Impaired cognition may be consciously pretended (malingered) for various types of gain. The effects of trivial head injuries may be magnified to escape hard labor or to gain monetary compensation. Mental status examination and neuropsychological testing of an individual who is feigning impaired cognition show inconsistent deficits, with better performance on many items that call for high-level integration than on some items calling for lesser levels of cognitive function. For example, simple similarities will seemingly not be understood, whereas more complicated similarities will call forth an abstract response; similarly, digit span, a simple test of attention, will be limited to three digits, whereas the patient can follow complicated directions to the restroom. Attempts have been made to develop a formal set of criteria for the detection of malingered cognitive malfunction (Slick et al. 1999).

Senile Squalor

The phenomenon of senile squalor is well known to those who work with elders. Termed by Clark et al. (1975) the Diogenes syndrome and recently reviewed by Badr et al. (2005) and Snowdon et al. (2007), senile squalor consists of self-neglect or neglect of one's surroundings, accompanied by hoarding and social isolation to which the individual is completely oblivious. The place of residence is disorganized, dirty, and filled with useless objects or materials. The exterior of the residence is usually dilapidated as well. At times, numerous animals described as "pets" are also in the dwelling and not well cared for. Attempts have been made to understand this phenomenon in terms of psychiatric disorders such as obsessive-compulsive personality or disorder, but most individuals with this set of behaviors functioned well earlier in life. It seems likely that these individuals suffer significant frontal brain circuit deficits of various origins. Studies such as functional neuroimaging have not been performed on these individuals because of their general unwillingness to participate in medical investigations. Also, longitudinal observations of these individuals have not been possible, as they generally refuse follow-up by social agencies. Following is a fairly typical case.

Case 4

An 83-year-old woman was referred for psychiatric evaluation because her neighbors complained that she was urinating in her backyard. She was seen in her home, which was completely filled with second-hand clothing. Clothes were approximately 2 feet deep, covering all of the floors, and the piles rose to approximately 5 feet near the walls, so that one could only navigate through the house by walking on trampled-down paths of clothes. The front door was totally obstructed; the back door could be opened only about 18 inches. Rat droppings were noted on the attic stairs. No bed was visible. Neighbors complained that she had slept in her car during hot weather. She stated that she slept wherever it was comfortable.

Approximately 1 year earlier, the woman's water heater had begun to leak, so she turned off her water supply to avoid flooding the house. Due to the cluttering of the house, a repairman could not access the hot water heater. She therefore had no running water since then. Because her toilet did not function, she urinated in a can that she emptied in the yard and also used public toilets. She stated she bathed at friends' houses or washed in public restrooms. It was unclear when she had last bathed, but she was not malodorous. Because she could not use her kitchen, she ate out for all meals.

The woman's grandson (her only living relative other than his children) stated that she had been hoarding for 30 years but that he had not been aware of its extent. He had last been in her home 15 years earlier. She had apparently discouraged visits to avoid revealing the extent of her hoarding. The grandson said that she had repeatedly refused assistance with clearing out her home.

When asked why she had allowed so much to accumulate, she stated that she had intended to clean it up for some time but that her accumulation had grown to the extent that she could no longer physically handle the task. She was surprised that others were concerned about her hoarding or lack of running water. She believed that her solutions to toileting and bathing were reasonable and practical.

She appeared to function independently in eating, bathing, dressing, and toileting, as well as in many of her instrumental activities of daily living, which included financial management (except as distorted by constant acquisition of unneeded objects) and using the phone. She was still driving. She had no history of mental illness (other than hoarding) or substance abuse. She was taking no medications.

On examination, the woman was well groomed, calm, and cooperative. Her speech was normal in rate, volume, and tone. She had no psychomotor abnormality. Eye contact was normal. Her affective responses were neutral to mildly sad. She appeared a little disconcerted to have so many people suddenly involved in her life; however, she joked and laughed at several points during the interview. She was alert and oriented to name, location, year, month, and day of week. She did not know the date. Her intellect was judged to be average. Her thought processes were clear, logical, and goal directed. No suspiciousness or psychotic symptoms were elicited. She reported that she slept well and had good appetite and energy, and she denied depressed mood. She was able to name two of her three grandchildren and stated that the third was a new baby whom she had seen only rarely. She scored 28 of 29 points on a prorated Mini-Mental State Examination (she was not asked her present location), missing only the date. She was able to name the U.S. president but not the preceding president. Confrontational naming was normal, as was clock drawing. She had mild difficulty with similarities. She reported the similarity between a cat and a rabbit as "enemies," and a motorcycle and a train as "speed demons." When asked what she would do if a fire started in her house, she replied that she would break a window out. Notably, she did not think her behavior at all peculiar.

Speech and Language Disorders

Disorders of speech and language occur in cognitive disorders. Speech refers to the mechanics of producing words, including the rate of speech and the placement of organs of speech, such as the larynx, glottis, jaws, and tongue. Speech tends to be slow in diseases of the basal ganglia, Parkinson disease, and vascular dementia; explosive or slurred in progressive supranuclear palsy; and poorly articulated in multiple sclerosis or following stroke. Language is the meaningful content of speech. Disorders of language (aphasias) often result from regional brain damage and may or may not be accompanied by more general cognitive impairment, although they are often confused with dementia. The history of aphasia patients usually reveals a brain insult, most often due to stroke or head trauma. Typical neurological deficits include hemiparesis (especially of the Broca type), unilateral hyperreflexia, and visual field deficits. In general, anomia that progresses to aphasia suggests neurodegenerative disease, whereas aphasia that resolves over time to anomia generally results from acute brain injury.

The categorization of aphasias is based on the language functions (e.g., fluency, comprehension, repetition) that are impaired (see Figure 3–2). Global aphasia impairs all language functions and results from large left-hemisphere strokes. Anomic aphasia, by contrast, primarily affects word finding, may be related to lesions of the left angular or left posterior middle temporal gyrus, and is common in Alzheimer disease. Broca (anterior, nonfluent) aphasia impairs verbal fluency, repetition, and naming and results from lesions of the posterior inferior portion of the left (or dominant) frontal lobe (Benson 1985).

In Broca aphasia, speech requires great effort and is agrammatical, with omitted word modifiers such as articles, prepositions, and conjunctions. For example, a person who wants to go to the bathroom might say, "Want… go…bath…room," with great effort and great relief after having expressed himself or herself. These patients generally understand what is said to them and can obey commands but have difficulty with repetition, reading aloud, and writing. Although they have difficulty with naming, they are helped by prompts.

Patients with Wernicke (posterior, fluent) aphasia have fluent speech (i.e., it flows well), but it is paraphasic and neologistic, and these patients demonstrate poor comprehension, repetition, and naming. The naming difficulty is not usually aided by prompting. Reading and writing are also impaired. Speech tends to have little in-

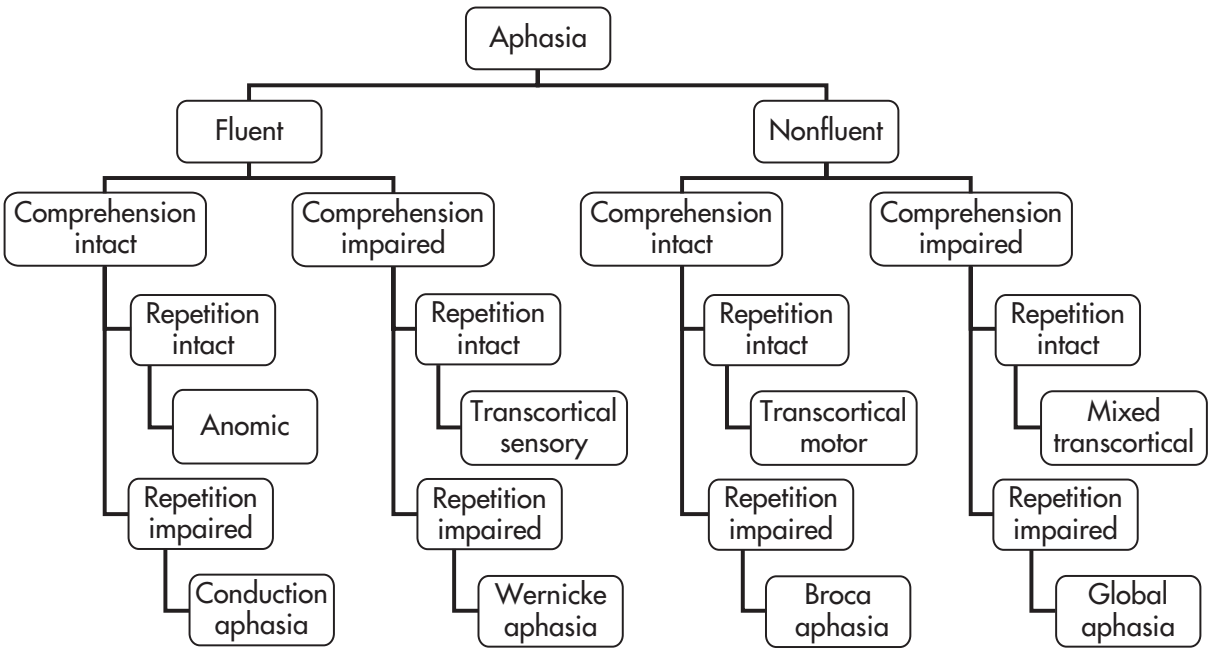

FIGURE 3–2. Differential diagnosis of aphasia.

formational content and relies on indefinite words and phrases. The sentence "I want to go to the bathroom" might be rendered by a patient with fluent aphasic as "I wish to go to the you-know bath place now soon," with no awareness of the peculiarity of his or her speech. Word approximations (paraphasias) may be based on similar sounds or phonemes (phonemic paraphasia), such as "meek" for *meat*, or similar meanings (semantic paraphasia), such as "writer" for *pencil*. The tissue damage in this syndrome is to the posterior superior portion of the first temporal gyrus of the dominant hemisphere.

Other aphasia syndromes are transcortical motor (impaired fluency and naming), transcortical sensory (impaired comprehension and naming), conduction (impaired repetition and naming), and mixed transcortical aphasia. The latter, which is a combination of transcortical motor and transcortical sensory aphasias, leaves patients able only to echo speech (Cummings 1985).

Among the frontotemporal dementias are progressive aphasias without history of brain insult or localizing neurological signs. They include primary progressive aphasia and semantic dementia (Kertesz and Munoz 2003; Mesulam 2003). For more detailed discussions of primary progressive aphasia and semantic dementia, see Chapter 5 of this volume and Chapter 12, "Frontotemporal Dementia."

Dysnomia, or mild difficulty with retrieval of nouns, occurs early in the course of Alzheimer disease. Later in the disease, more pronounced language disturbances occur, including fluent aphasia, perseveration, palilalia (echoing one's own speech), and possibly mutism. Figure 3–3 presents an algorithm for the differential diagnosis of cortical dementias. It differentiates the language presentation of primary progressive aphasia and semantic subtypes of frontotemporal dementia from the language disturbance in the general category of frontotemporal dementia. For example, in response to a request to write a sentence, a man with Alzheimer disease who had prominent language dysfunction wrote the following:

> Sou you can right so he can write this is zold This is so some belt so the right food can you can right so can rin so you can right the right So you can right so that you can right.

Clinical Techniques and Tools for Diagnosing Cognitive Dysfunction

Clinical evaluation of a patient includes history taking and direct examination. Cognitive and behavioral history and mental status examination establish the presence of cognitive dysfunction; medical history and neurological examination help to determine its etiology. History taking involves the patient, a knowledgeable informant, and all pertinent medical information. Direct access to medical records is important because lay informants often do not

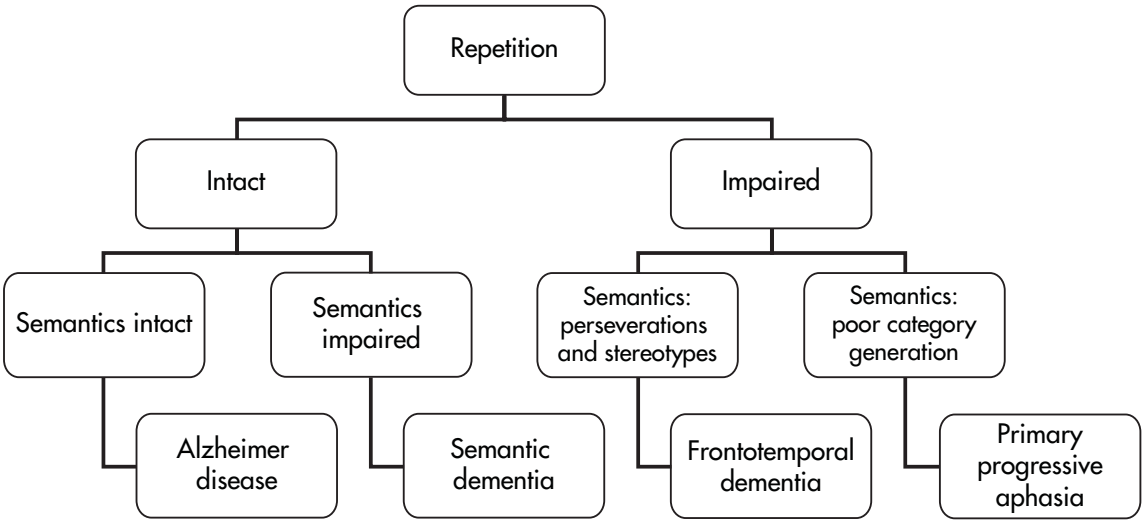

FIGURE 3–3. Language algorithm for the diagnosis of cortical dementias.

accurately recall medical events or the outcomes of various laboratory tests. In the case of very old nursing home residents, the only available information may be from the nursing home staff and records.

In addition to eliciting information concerning patients' cognitive abilities, the interviewer seeks evidence of emotional or interpersonal contributions to the presenting symptoms, evaluates patients' emotional responses to their mental difficulties, and attempts to determine family strengths and weaknesses. Patients' personality patterns are also considered. This information helps in shaping the plan of management, even if treatment of the underlying brain disorder is not possible.

History Taking

Ideally, the clinician should gather and review the patient's medical records in advance of examining the patient. When possible, we obtain a history from a family informant before the first visit by telephone or by mail using our History Form (Appendix A) and our Level of Function Scale (Appendix B). We also ask what medications the patient is taking and often request that patients and their families bring all the medication in the family medicine chest. This information helps to focus history taking and the mental status examination. We also elicit personal and medical histories directly from the patient and accompanying friends or family members.

When possible, patients are accompanied by a family member and interviewed in the presence of that person to ensure the accuracy of factual information. Patients are interviewed alone if unaccompanied or if they object to the presence of others in the examination room. When possible, time is allowed to interview the accompanying person alone; family members or friends often withhold information in a patient's presence out of concern that they may humiliate or anger the patient. Typical information withheld concerns patients' paranoid thinking, hallucinations, or incontinence.

Having a friend or relative present is a comfort to most persons with cognitive impairment. Thus, history taking tends to be a three-way conversation rather than a formal interview. In the flow of the conversation, many clues emerge concerning the relationship between patients and significant others, the impact of patients on their families, and the impact of others on the patient. Husbands often resent their wives' diminished ability to maintain the household. Dependent spouses may resent having to be responsible for their formerly dominant spouses. In many cases, there is tension between spouses because one does not believe that the other truly cannot learn, remember, or understand. For example, a man who knew his wife had Alzheimer disease chided her for reading romance novels instead of the more substantial reading she had done earlier in her life. Examining one spouse in the presence of the other can be helpful in dealing with the intact spouse's denial and in demonstrating how to deal with defects in the other's ability to remember, plan, and cooperate.

Mental Status Examination

The mental status examination helps to establish the probable presence or absence of a cognitive disorder and may also suggest the nature of the underlying brain or sys-

temic disease. (For a highly detailed mental status examination, see Strub and Black 2000.) The mental status examination contained in Appendix C is employed at our clinic, where we customarily perform a neurological examination as well (see Appendix D). Both can ordinarily be accomplished during a 90-minute visit if historical and medical information has been gathered and reviewed in advance.

The clinician performs the mental status examination (with the patient's consent) in the presence of any accompanying persons. During this time, the clinician forms tentative hypotheses as to how far patients can be pushed to perform and how to best support their coping and defense mechanisms while simultaneously obtaining the needed information.

The mental status examination is performed with consideration for a patient's frustration tolerance and is also tailored to his or her level of cognitive performance. For example, when it becomes obvious that a patient is not oriented to year and month, we do not usually inquire about orientation to day and date. When the patient is irritable or easily frustrated, we abbreviate each category of inquiry. We treat all responses as equally valid, whether correct or not, and praise the patient for effort by saying "good" or "that's fine" after a series of responses. Exceptions to this general approach are in the formal testing of cognition for scientific studies, when completeness is important, or when we suspect that the patient is not making an effort to perform the task, and we may either withhold praise until the patient has made adequate effort or urge the patient to focus attention on the task at hand.

Attention is tested by using forward and reverse digit span. Working memory is tested by asking a patient to recall three words following 5 minutes of distraction; this test can be performed with objects presented verbally (verbal memory) or objects shown to the patient without naming them (visual memory). Response to cuing is also important because it helps to distinguish retrieval deficits from failure to encode. Testing remote memory is more difficult. A patient with little formal education can be asked about current events that fall within his or her range of interest; this is done most effectively when an outside informant is asked about recent events in the patient's life (e.g., family birthdays and other family events).

Routine examination of language function includes assessment of articulation, fluency, comprehension, repetition, naming, reading, and the ability to write sentences (see the section that follows for a more detailed language examination). Assessment of language fluency encompasses delays in word finding, paraphasias, and neologisms. Word fluency (the ability to generate a list of words), a very sensitive indicator of cognitive impairment, can be tested by asking patients to name all the animals they can think of in 1 minute. The average score is 18±6 (Goodglass and Kaplan 1972). Comprehension tests begin with graded tasks, asking patients to point to one, two, and three objects in the room, followed by asking simple logic questions, as indicated in Appendix C. Naming tests should include the parts of objects, such as the parts of a watch (stem, watchband, back or case, face, crystal or glass) or the parts of a shirt. A useful office test for naming ability is the Boston Naming Test, which has a 15-item short form (Goodglass et al. 2001). Reading ability should be considered in the context of patients' education. Writing ability is assessed by asking patients to write a dictated sentence and then to compose a sentence of their own.

We test calculating ability using a simple multiplication problem.

Praxis is evaluated by asking patients to imitate an action performed by the examiner, to perform simple motor acts in response to the examiner's request, and to copy a set of simple geometric figures (see Appendix C). The task of drawing a cube is used to detect constructional dyspraxia in mildly impaired, well-educated persons. In our experience, cognitively intact persons age 80 years or older cannot draw the cube well.

Fund of information is assessed by using a standard set of questions ranging from simple to difficult. The responses are evaluated in relation to a patient's level of education and job achievement.

A patient's ability to think abstractly is assessed by using similarities and proverbs, but this part of the examination requires consideration of the patient's education, cultural background, and native language. Impairment of abstract reasoning can be inferred from part-object substitution in tests of ideomotor praxis, such as using one's fingers as the teeth of a comb while pretending to comb one's hair or using one's finger as the match when pretending to blow out a match. Judgment may be estimated by asking patients questions about how they would manage certain life situations, such as, "What would you do if the electric company called and told you that the last check you wrote them was returned because of insufficient funds?" However, judgment is probably better assessed from a history by an informant than by direct evaluation of the patient.

Elements of the mental status examination that detect executive dysfunction include ideomotor and constructional praxis, abstract reasoning, and judgment. Portions of the neurological examination, including the Luria hand sequence, go–no go tasks, and tests for impersistence, also help in detecting executive dysfunction. Clock drawing is another useful test of executive function. Executive dysfunction is also detectable in the course of the history

taking (e.g., mistakes in social judgment such as inappropriate sexual advances) and in the course of the mental status examination (e.g., inappropriate handling of objects such as grasping the examiner's tie, or inappropriate laughter or flirtation).

Examination of Language

An important but underutilized aspect of the mental status examination is language evaluation. To perform a basic language evaluation, the clinician needs nothing more than sensitivity to articulation, fluency, repetition, grammar, and semantics. The question-and-answer format of the mental status examination lends itself to the evaluation of language skills.

A basic language evaluation samples spontaneous speech, comprehension abilities, repetition and prosody, naming, and category generation. Spontaneous speech is usually elicited during the history taking. Language evaluation can also be accomplished by asking patients to describe standard stimuli such as the "cookie theft" picture in the Boston Diagnostic Aphasia Examination (Goodglass et al. 2001) or any drawing or photograph. Language expression and comprehension can be assessed in a graded fashion; naming of pictures can be graded by starting with a common object (e.g., an automobile) and later showing an uncommon object (e.g., a hammock). Naming ability can progress from pointing to one object to pointing to a series of objects. Repetition ability is tested with gradually more complicated utterances, beginning with single words and extending to phrases, sentences, and several-sentence statements. Patients are asked to generate word lists to test their ability to generate categories (name all the animals you can think of in 1 minute), a type of semantic task. Assessing patients' reading and writing of sentences is useful as well.

The articulation of speech is a function of both motor speech skills and language abilities. Imprecise placement of the various structures in the mouth will produce disordered speech. Disruptions in the motor cortex and the language cortex of the brain will result in misarticulation. The difficulty is apparent in patients who use the wrong sound for letters in words, such as a "b" sound for a "v" sound. Articulation problems are rare in cortical dementias and suggest etiologies due to other problems, such as stroke, that may affect the motor cortex or motor tracts. A phonemic paraphasia is the substitution of one sound in a word for another, as in /pot/ for /cot/. Verbal apraxias manifest as searching to find the correct placement of sounds, such as /pot, lot, rot, cot/; this reflects an inability to place the tongue properly to form sounds accurately. Evaluating this function can be done using a list of words incorporating the consonants and vowels of English (Fudala 2001). For screening purposes, a pattern of misarticulations in pronunciation indicates possible other etiologies of dementia and can be assessed by speech or neuropsychological testing.

Fluency is the rhythm and intonation of a speaker's sounds and phrases. Deficits in fluency include halting speech, long pauses, interjections while searching for words, stuttering, and monotonous tone of voice. Many words are completely eliminated in dysfluent speech, giving it the character of "telegram speech." Articles, function words, conjunctions, and prepositions all may be lost, and the listener is left with a bare set of content words. For instance, dysfluent speech will have decreased verbal output, decreased phrase length, effortful speech, and loss of prosody (e.g., "I go store").

Repetition is the ability to hear and imitate immediately what is spoken. This requires an intact hearing mechanism, an intact articulatory inventory, and fluent speech (if the stimulus is longer than a word). Problems with repetition will result in an inability to repeat a word, phrase, or sentence immediately after it is said.

Grammar is the framework in which the meanings of words are recognized. Each grammatical form has a purpose. Sentences are a series of blank spaces in a framework into which words are placed. For example, a verb conveys action or being. It tells whether the subject of the sentence acted or was acted upon (active or passive voice), the number of subjects, and the time at which action occurred (tense). Agrammatic speech may result in mismatches between subjects and verbs due to a misuse of person, number, and gender markers (e.g., "Me go store").

Semantics refers to the meaning system of words, phrases, and sentences. The competent speaker is able to access the spoken word's form and the meanings of that word. Semantics is a set of acceptable interpretations to each entity we accept as a word or a sentence, to include words that fit the intent of the speaker and convey the message most easily to the listener. For example, the word *can* is the verb meaning "to be able to" or the noun meaning "a receptacle made out of tin." Generating interpretations of ambiguous sentences is one way of testing for semantic abilities. In ambiguous sentences, the multiple meanings of a word can generate several interpretations for a sentence's meaning (e.g., the sentence "Children hate annoying parents" could mean "Children hate to annoy their parents" or "Children hate parents who annoy them"). Naming objects in pictures or generating names in a given category are other ways to assess semantic abilities.

Persons with early Alzheimer disease have generally intact language. The abilities to articulate, to form grammatical sentences, and to repeat are not affected until late in the disorder. The first sign of language disturbance typ-

ically occurs at the semantic level with the inability to retrieve words, although the meaning of the words is retained.

Speech in frontotemporal dementias may become markedly less fluent and slower, and the speaker has obvious grammatical struggles. These problems gradually worsen, as does language function in all the cortical dementias in the middle and late stages. Mutism is the end point of language function in long-term dementia survivors.

In primary progressive aphasia, a clinical type of frontotemporal dementia (Kertesz and Munoz 2003) (see also Chapter 12 of this volume), phonological errors in speech are evident early (e.g., saying /efelant/ for *elephant*). Anomia is initially mild. Comprehension is relatively good. Suggested diagnostic criteria include the gradual loss of word finding, object naming, syntax, or word comprehension abilities in the absence of stroke or tumor, with loss of day-to-day function attributable to loss of language abilities. Loss of syntax and loss of word-naming abilities both cause speech to be slow and deliberate.

In the semantic dementia presentation of frontotemporal dementia, the patient has relatively intact syntax and phonology/pronunciation skills but a marked inability to generate words in a semantic category. Category fluency is reduced to being able to generate, for example, less than 12 animal names in a minute. The ability to determine semantic relationships between pictures, as in the Pyramids and Palm Trees Test (Howard and Patterson 1992), is poor. In this type of test, which can be done with pictures cut out from magazines, patients are asked to give the connection between groups within a similar category (e.g., camels and pyramids).

Pragmatics is the level of language concerned with language use in general. Word meaning changes with use (e.g., "He will see me about this" might take on different meaning if *this* can refer to more than one thing). Pragmatics involves conversational implications; how two individuals use the rules of conversation affects the meanings of their utterances in a conversation. Rules of conversation involve turn taking, appropriate pauses, topic shifting, and topic maintenance. Another feature of pragmatics of language is presupposition—that is, a sharing of "background assumptions" between speakers in a conversation that affects comprehension (Bayles and Kaszniak 1987, p. 167). For example, talking about airplane schedules presupposes that the listeners know what airplanes are and how they work.

Repetition is typically intact in Alzheimer disease and semantic dementia but very poor in primary progressive aphasia. An example of a repetition task is having a person repeat three words, then three phrases, and finally three simple sentences.

If needed, more detailed language evaluation can be conducted by a neuropsychologist or a speech pathologist.

Characterizing Dementing Illnesses

Dementing illnesses can be characterized as *cortical* or *subcortical* (see also Chapter 5 of this volume). Patients with cortical dementias usually present as one of two overlapping groups: *frontotemporal* or *temporoparietal*. Frontal dementia can be due to Pick disease or anterior cerebral artery stroke, but it occurs less frequently in Alzheimer disease. Common frontal symtpoms are progressive personality change and breakdown in social conduct (Neary et al. 1998). Other features include defective judgment, difficulty in focusing attention, apathy, disinhibition, silliness, echoing words, mirroring others' behavior, unawareness of deficit, difficulty in following instructions (often manifested as motor dyspraxia), and often a slightly prancing gait. Personality changes often antedate cognitive symptoms in frontotemporal dementias; Miller et al. (1991) found social withdrawal and behavioral disinhibition to be the earliest symptoms. In primary progressive aphasia, initial symptoms include difficulty with verbal expression. Normal pressure hydrocephalus often appears with frontal signs, such as complete indifference to urinary incontinence. Temporoparietal dementia, the most common symptom of Alzheimer disease, is accompanied by naming difficulties and constructional dyspraxia, with relative preservation of personality. Persons with cortical dementias may or may not be aware of their deficits.

Subcortical dementias, with primary pathology in the thalami, basal ganglia, rostral brain stem, and their frontal projections, overlap in symptoms with frontal dementias but also usually involve speech and motor abnormalities. The most prominent symptoms include overall slowing of movement and cognitive processing, and deficits in social judgment and mood change. Causes of subcortical dementia include cerebrovascular disease, Parkinson disease, Huntington disease, Wilson disease, and progressive supranuclear palsy (Cummings 1990).

Quantifying Aspects of Dementing Illness

Clinicians generally rely on impressionistic data to make diagnoses and to follow the course of an illness and its treatment. They also employ objective measures, such as pulse, temperature, blood pressure, hematocrit, and blood urea nitrogen concentration. Growing awareness of the potential reversibility of some dementias and the potential for treating cognitive disorders has led to the development of instruments to quantify the phenomena associated with them, including overall functional ability; cognition; and behavioral, emotional, perceptual, and ide-

ational symptoms. We describe some clinically useful scales in the remainder of this section. Readers interested in other scales for quantifying aspects of dementia are referred to the compendium of assessment instruments assembled by Burns et al. (1999).

Measures of Global Function

For day-to-day office use, we employ an unstandardized scale devised by Ms. Kristin Martin-Cook at the University of Texas Southwestern Medical Center to obtain a rough estimate of the patient's level of function that is adequate for clinical purposes (Appendix B). It is mailed to the patient's family to be completed independently of the patient and is returned to us before the patient's first visit. For research purposes, the most commonly employed global instrument is the Clinical Dementia Rating (Morris 1993), which requires a skilled interviewer and separate interviews of patient and caregiver.

Measures of Cognitive/Executive Function

The Mini-Mental State Examination (MMSE; Folstein et al. 1975), administered directly to the patient, is the most widely used brief cognitive assessment tool. It requires 10–15 minutes to administer and samples orientation, attention, concentration, recent memory, naming, repetition, comprehension, ideomotor praxis, constructional praxis, and the ability to construct a sentence. A perfect score is 30 points. The MMSE is confounded by premorbid intelligence and education. The originators indicate that a score of 23 or below by someone with a high school education is suggestive of dementia. A cutoff score of 18 or below is suggested for those with an eighth-grade education or less. A population-based study showed an inverse relationship between test score and education. The median score was 29 for unscreened individuals with at least 9 years of schooling, 26 for those with 5–8 years of schooling, and 22 for those with 0–4 years of education. The same study showed an inverse relationship between age and test score, with a median of 29 for those age 18–24 years and a median of 25 for those age 80 years or older (Crum et al. 1993). The MMSE is not a sensitive test; it does not examine executive function and frequently does not detect impairment in highly educated persons. However, its brevity and the minimal training required for its administration make it especially useful in conjunction with the clock-drawing task (see next paragraph) as a general screening of cognitive impairment and for following the progression of cognitive disorders. (The MMSE is protected by copyright and must be ordered from Psychological Assessment Resources.)

The clock-drawing task is a simple means to detect executive dysfunction, because the task involves planning, sequencing, and abstract reasoning. Of the many ways to administer and score this task, we prefer the method of Nolan and Mohs (1994) for routine office use. The subject is presented with a blank page and asked to draw the face of a clock and to place the numbers in the correct positions. After drawing a circle and placing the numbers, the subject is asked to draw the hands so they indicate the time as 20 minutes after 8. Scoring is as follows: 1 point for drawing a closed circle, 1 point for placing numbers correctly, 1 point for including all correct numbers, and 1 point for placing the hands in the correct positions. There is no cutoff score, but any score below 4 raises the suspicion of executive impairment. Distortions due to tremor are disregarded. Figures 3–4 and 3–5 show deficits in persons diagnosed clinically with Alzheimer disease whose MMSE scores were within the normal range for their age. Figure 3–4 shows the improper placement of the clock hands on the drawing of a person with early Alzheimer disease who scored 27 points on the MMSE. Figure 3–5 shows the clock drawn by a person with early Alzheimer disease who scored 28 on the MMSE but was unable to find 20 minutes after 8 on the clock, and wrote in "20."

Measure of Activities of Daily Living

The Alzheimer's Disease Cooperative Study: Activities of Daily Living Inventory (Galasko et al. 1997) is used in drug trials for Alzheimer disease. It is valid and reliable. Scores for the 23-item version (Appendix E) range from 0 (completely dependent) to 66 (completely independent). This instrument, which is administered to a knowledgeable informant, requires about 20 minutes. There are no norms for this measure.

Measures of Neuropsychiatric Symptoms

The following two tests are used to detect and quantify various behaviors. Normal ranges have not been established for either of them.

The Neuropsychiatric Inventory (Cummings et al. 1994) (see Appendix F) was designed to assess the entire range of psychopathology in individuals with cognitive impairment. The inventory includes probe questions concerning delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behavior disturbances, and appetite/eating changes (Cummings 1997). It also includes a measure of caregiver distress (Kaufer et al. 1998). If the response to a probe question is positive, further questions are asked. If

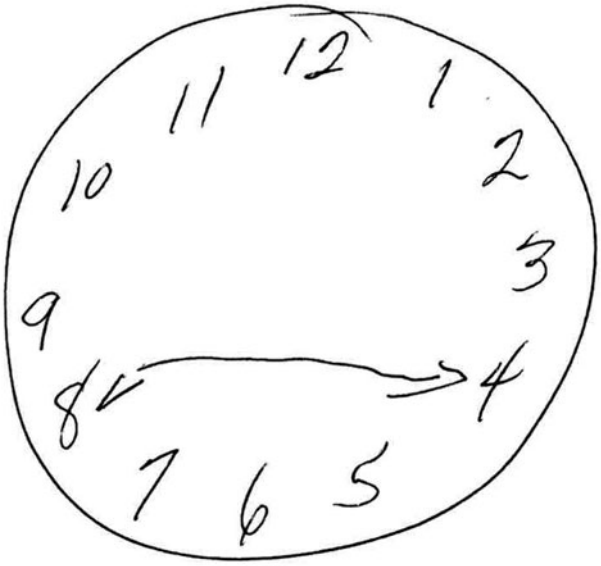

FIGURE 3–4. Clock drawn by early Alzheimer patient with Mini-Mental State Examination score of 27.

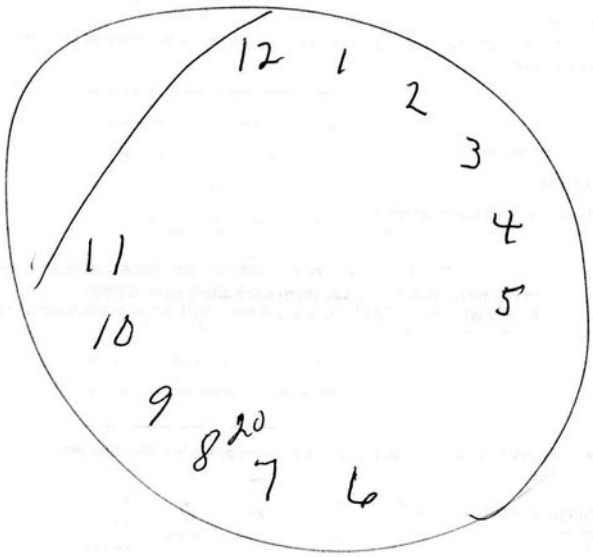

FIGURE 3–5. Clock drawn by early Alzheimer patient with Mini-Mental State Examination score of 28.

the response is negative, the examiner proceeds to the next domain. A nursing home version has also been created, but the authors caution that it is best administered by trained research personnel (Wood et al. 2000). Because of its design, the instrument can be administered in 5–10 minutes by an experienced technician or clinician. It is a good general screening tool and can also be used to follow the course of treatment.

The Agitated Behavior in Dementia Scale (Logsdon et al. 1999b) (see Appendix G) is a 16-item instrument administered to caregivers. It has a 2-week window of observation. The scale evaluates the frequency of and caregiver reaction to common agitated behaviors in community-dwelling persons with Alzheimer disease. It evaluates those behaviors rated as most problematic in persons with mild to moderate dementia that can be observed and described objectively. Administration time is about 15 minutes. This instrument is also useful for tracking response to treatment.

Measures of Quality of Life

The impact of treatments on patients' quality of life is as important as it is on patients' symptoms or underlying disease. Because quality of life is subjective, it can be measured directly only in persons with relatively mild cognitive impairment. Persons with severe cognitive impairment are often unable to perceive or report on quality-of-life issues. The scales described below appear to have the most promise for clinical trials.

The Quality of Life in Alzheimer's Disease Scale (Logsdon et al. 1999a) (see Appendix H) is a 13-item instrument that can be administered directly to persons with Alzheimer disease or other forms of cognitive impairment. When administered directly, it is reliable for persons with MMSE scores between 10 and 28. The scale can also be given as a self-completed questionnaire to a caregiver surrogate. Each item is rated on a 4-point scale from *poor* to *excellent.* The patient and caregiver scales may be scored independently or may be combined by multiplying the patient score by 2, adding the caregiver score, and dividing by 3, thus giving more weight to the patient report. The scale has a 1-week window of observation. Administration time is about 15 minutes. Spector et al. (2003) found the scale to be sensitive to the effects of a cognitive stimulation program for elders with dementia.

The Quality of Life in Late-Stage Dementia Scale (Weiner et al. 2000) (see Appendix I) is an 11-item scale with a 1-week window of observation. Items consist of observable behaviors such as smiling, crying, and apparent enjoyment of interaction with others. It is administered to family or professional caregivers. Administration time is about 5 minutes. The scale is sensitive to change and can be used in treatment studies (Martin-Cook et al. 2005).

Conclusion

Despite numerous advances in diagnostic technology, the skilled clinician is still the most useful instrument in our

diagnostic armamentarium. No amount of technology can replace the skilled clinician's ability to establish the rapport needed to take an adequate history and examine the patient, to perform the diagnostic workup in such a way as to maintain the cooperation of the patient and family, and to determine the best way to present the findings of the evaluation. The clinician, having placed the patient's symptoms in context, helps patients and their families decide what course of action best fits them at this point in their lives. The development of these essential skills is beyond the scope of this book, but is hopefully encompassed in the training of psychiatrists to recognize that the pathology we treat is part of a person and that the outcome of our treatment depends in large measure on our skill in dealing with the person within the context of his or her social network.

KEY POINTS

- Cognitive impairment is detected from patient history and mental status examination. Due to increasing precision in diagnosis, clinicians are better able than in the past to determine the underlying brain or systemic pathology in persons with cognitive impairment.
- Cognitive disorders encompass neuropsychiatric symptoms (e.g., behavioral, emotional, vegetative, ideational, and perceptual disturbances).
- Assessment of language can add greatly to the differential diagnosis of cognitive disorders.
- Instruments are available to identify and quantify the cognitive and neuropsychiatric symptoms for both routine clinical and research purposes.

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CHAPTER 4

Medical Evaluation and Diagnosis

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The following are cognitive-related indications that a patient should be seen for clinical evaluation or reevaluation: subjective complaints of cognitive impairment, the objective development of cognitive impairment, or the sudden worsening of cognitive impairment or behavior in a person diagnosed with dementia. Some of the important elements of an evaluation of cognitive dysfunction are summarized in Table 4–1; additional medical studies used for select patients are listed in Table 4–2. The extent of the evaluation depends on the physician's assessment of the problem, the facilities available to undertake a diagnostic evaluation, and the cost-benefit ratios of the various diagnostic procedures available. One important reason for undertaking a medical evaluation is the possibility of finding a reversible cause of the cognitive impairment. Fully reversible dementia syndromes are rare, but an important goal of clinical assessment is to identify causes of cognitive dysfunction that are at least partially reversible. Reversible cognitive impairment is most often due to depression, medications, or hypothyroidism. Correct diagnosis of cognitive impairment is essential to guide management, even in irreversible conditions, and to provide important prognostic information for patients, families, and medical professionals.

In addition to evaluating the etiology of cognitive impairment, the value of a complete medical evaluation is to ascertain an individual's overall health status. This helps the patient and family optimally manage other problems that may have an impact on the individual's functional state (Rubin 2006).

Barry and Moskowitz (1988) suggested that, in general, evaluation of cognitive impairment should be undertaken with the goal of improving patient quality of life rather than simply identifying disease. On the other hand, the number of untreatable diseases is shrinking, and precise diagnosis is important in deciding which medications to prescribe or avoid. For example, anticholinergic drugs may aggravate cognitive impairment in patients with Alzheimer disease by increasing the preexisting cholinergic deficit.

Three main groups of individuals present for cognitive status evaluation. A few (usually self-referred) seek evaluation because of a family history of Alzheimer disease or concern about subtle cognitive changes that may be re-

TABLE 4–1. Medical evaluation of cognitive dysfunction

History and physical examination
Neurological examination
Mental status examination
Attention and concentration, recent and remote memory, language, executive functioning, visuospatial skills
Mini-Mental State Examination or comparable objective screening measure
Assessment of mood
Blood tests
Blood chemistries (electrolytes, blood urea nitrogen, creatinine, glucose)
Complete blood count and differential
Folate
Homocysteine
Lipid profile
Serologic tests for syphilis (rapid plasma reagin and treponemal test), if indicated
Thyroid stimulating hormone
Vitamin B_{12} level
Computed tomographic or magnetic resonance imaging of the brain

lated to aging or a medical or psychiatric condition. The second and largest group comprises those persons brought for evaluation by concerned friends or family members. Virtually all of these individuals have dementing illnesses of which families and friends are aware. These families seek second opinions for various reasons, including the wish to explore every possibility of uncovering a treatable cause for cognitive impairment or to find treatment for a dementing illness that had previously been described as untreatable. The third group includes individuals with preexisting cognitive impairment who experience sudden functional or cognitive decline or develop troublesome neuropsychiatric symptoms.

Different medical evaluations may be indicated for a subjective complaint of cognitive impairment, for the initial evaluation of a person whose friends and family have noted signs of cognitive impairment, and for the follow-up evaluation of sudden cognitive deterioration in an adequately diagnosed dementia patient. A subjective complaint of cognitive impairment that is unsubstantiated by an outside informant nevertheless requires a medical and psychiatric history, a formal mental status examination, and a general physical examination, including neurological examination and routine screening laboratory tests. If the history and mental status examination do not confirm cognitive impairment and no brain damage is evident, psychiatric evaluation and neuropsychological testing may be indicated. The com-

TABLE 4–2. Medical evaluation of cognitive dysfunction—additional measures

Neuropsychological testing
Blood tests
Antinuclear antibodies
Calcium
Ceruloplasmin
DNA studies (prensenilin 1, CAG repeats, ataxia profile)
Erythrocyte sedimentation rate
Human immunodeficiency virus/Liver function tests
Magnesium
Methylmalonic acid
Paraneoplastic antibodies (anti-Hu, anti-MaTa, anti-Ri, anti-Yo)
Porphyrins
Vasculitis workup (protein C and S activity, activated protein C resistance, antithrombin III, factor V Leiden, lupus anticoagulant, prothrombin 20201 A)
Lumbar puncture
Routine studies (cell count and differential, total protein, glucose, VDRL, Gram stain, and bacterial culture)
Additional studies:
Amyloid beta and tau protein concentrations
Acid-fast bacillus stain and culture
Cryptococcal antigen
Cytology
Fungal culture
Immunoglobulin G index/synthesis rate
Lyme titer or PCR
Oligoclonal bands
Viral tests: titers and PCR (cytomegalovirus, herpes simplex, varicella zoster)
14-3-3 protein
Whipple antibody by PCR
Urine tests
Urinalysis
24-hour urine copper
24-hour urine heavy metals
24-hour urine porphyrins
Toxicology screen
Electroencephalogram
Cisternogram
Arteriography (invasive or noninvasive)
Single photon emission computed tomography (SPECT)
Positron emission tomography (PET)

Note. CAG=cytosine-adenine-guanine; DNA=deoxyribonucleic acid; VDRL=Venereal Disease Research Laboratory test; PCR=polymerase chain reaction.

plaint of cognitive impairment, like any other medical complaint, may be a means to deal with emotional issues and concerns (Weiner 1969), as illustrated in the following case.

Case 1

A 60-year-old woman complained of impaired memory and concentration. Her medical history indicated that she had been evaluated medically for several physical complaints with no definite findings. Her husband reported that he had not observed difficulty with her cognitive functioning. A complete battery of blood tests and a urinalysis were performed and were negative or within normal limits. A complete neurological evaluation, including computed tomography of the head and an electroencephalogram, was negative.

Neuropsychological testing showed no clinically meaningful impairment, but personality testing showed her to be highly anxious and highly preoccupied with physical symptoms. To the psychiatric examiner, she confided that her greatest problem was her husband's physical abuse, which she related to their chronic marital conflict. This patient was assured that she did not have a brain disorder and was helped to draw her husband into brief marital counseling.

The syndrome of mild cognitive impairment is characterized by subjective memory decline in the absence of functional decline. Persons with mild cognitive impairment often have no detectable cognitive deficits on routine office mental status testing, but testing of memory based on immediate and delayed recall of a paragraph-long narrative can reveal impairment (Petersen et al. 1999).

Setting

The medical evaluation of persons with cognitive impairment is generally performed in an outpatient setting. Hospitalization is required only when behavioral symptoms make outpatient evaluation impossible or when it is suspected that an emergency medical or surgical procedure might be needed, such as the emergency treatment of lupus cerebritis with bolus intravenous steroids or evacuation of a rapidly expanding subdural hematoma. Otherwise, hospitalization may actually have transient deleterious effects, because some individuals become more confused in a hospital environment (Etienne et al. 1981). A comprehensive multidisciplinary evaluation requires 1–3 days, depending on the efficiency of scheduling, the patient's tolerance, and the extent of medical and neuropsychological testing. In this chapter, discussion is limited to the medical aspects of the evaluation. (See also Chapter 5, "Neuropsychological Assessment in Dementia," and Chapter 6, "Neuroimaging.")

History

The diagnostic process begins with history taking. An adequate evaluation also involves obtaining information from collateral sources. It is useful to obtain prior medical and psychological records in advance to avoid duplication of tests and loss of information due to informants' lack of awareness or understanding of the diagnostic procedures that have already been employed or of medications prescribed. It is important to include a person with close knowledge of the patient in the diagnostic process and to request a list and/or bottles of all prescribed or unprescribed medications, including nonprescription medications and nutritional supplements.

The history of the present illness should be gathered with regard to the patient and family's chief current concern, the first cognitive and/or behavioral problem(s) noted, the course of the problem(s), and other problems that may have developed. In addition to the patient's age and handedness, the patient's level of education and current or prior occupation are important. A few patients are aware of their memory problems or other symptoms. Many do not report difficulties but are brought for evaluation because others have noted lapses in memory or judgment and are concerned.

An important question is whether the symptoms were acute, subacute, or gradual in onset. An acute onset (within minutes or hours) suggests delirium rather than dementia and requires a differential diagnosis based on consideration of infectious, toxic/metabolic, vascular, traumatic, psychiatric, or multifactorial causes. When caused by vascular problems, the symptoms may be due to ischemic stroke (secondary to embolization or atherosclerotic thromboembolic disease), hemorrhage (due to trauma, hypertension, aneurysm, amyloid angiopathy, and/or tumor), or vasculitis (including systemic lupus, temporal arteritis, and central nervous system vasculitis). In young adults developing schizophrenia, a catatonic episode may come on within hours. Malingered cognitive impairment and fugue states also develop suddenly (Lamb and Prigatano 2000), both usually occurring in the context of extreme environmental or interpersonal stress. Subacute onset (days to weeks) suggests infectious, toxic/metabolic, or neoplastic origin, whereas a gradual progressive decline over months to years is more typical of degenerative disorders.

Intermittence of symptoms occurs with all brain disorders and does not distinguish organic from functional disorders. The waxing and waning of symptoms over hours is typical of delirium. Dementing illnesses are also characterized by fluctuating symptoms, but the fluctua-

tions are less dramatic and are often more prolonged. There is often diurnal confusion that may or may not be associated with fatigue. Symptoms of all illnesses that produce cognitive impairment tend to worsen in unfamiliar environments or when emotional and cognitive demands increase. Although the phenomenon of *sundowning*—the worsening of symptoms as the day progresses—has been called into question as an intrinsic part of dementing illness (Cohen-Mansfield 2007), it is a common observation in persons with dementia.

It is often difficult to date the onset of cognitive or behavioral difficulties. A family may be unaware of any significant changes until a loved one is hospitalized for one reason or another. The combination of an unfamiliar environment and a medical illness or a surgical procedure often unmasks preexisting dementia and may also precipitate delirium in a person with cognitive impairment. Therefore, it is important to reevaluate the person for cognitive impairment once a delirium has resolved.

The following questions can help determine the onset and progression of cognitive and behavioral symptoms.

1. *How is the person's job performance? If the person is retired, was retirement due in part to impaired performance?* Has there been any change in the performance of usual activities (e.g., conversation and social interaction, housekeeping, meal preparation, operating appliances, making routine purchases, making change, writing checks, driving, dressing, grooming, performance in hobbies and social activities). When was the first change or loss of interest in these activities? Did symptoms precede or follow any significant medical illness or surgery?
2. *Are the symptoms progressive, diminishing, or stabilized?* Lack of progression suggests a single insult, such as a vascular accident, trauma, or depression. Progression may be associated with infectious diseases (acquired immunodeficiency syndrome [AIDS], Creutzfeldt-Jakob disease, neurosyphilis), trauma (subdural hematoma), metabolic disorder (diabetes), or neurodegenerative disorder. Neurodegenerative disorders such as Alzheimer disease, Parkinson disease, frontotemporal dementia/Pick disease, and multisystem atrophy have a relatively smooth downward course. Vascular dementia generally has a stepwise progression.

   Symptomatic improvement is associated with trauma, acute vascular disorders, and acute toxic and metabolic disorders. Fluctuations in cognitive dysfunction may occur in many types of dementing illness and are frequently associated with dementia with Lewy bodies (McKeith et al. 1996). In most dementing illnesses, cognitive impairment fluctuates depending on the complexity of the environment, emotional strain, fatigue, general physical health, and time of day. Symptoms are frequently worse in the evenings due to fatigue and loss of orienting sensory cues.

   Paroxysmal deterioration with relatively full interepisode recovery occurs in alcoholic persons with encephalopathy that is due to liver disease. Transient global amnesia is a syndrome of intermittent confusion of diverse etiology, probably due in many cases to ischemia of the medial temporal lobes. Partial complex seizures can cause intermittent behavioral disruption with cumulative chronic deterioration, but the history also reveals motor stereotypy and postictal sleepiness.
3. *Has the person experienced the same or similar symptoms in the past?* Past experience of short confusional episodes may suggest epilepsy or transient ischemic attacks. Periods of cognitive dysfunction lasting days or weeks may be related to emotional disorders, metabolic disorders such as porphyria, or diseases associated with Lewy bodies. Individuals who are malingering or in fugue states will often report similar previous episodes. Depressed persons may report similar episodes of cognitive impairment with past episodes of depression.
4. *Does the person have a history of psychiatric disorder or severe environmental stress?* An episode of depression, whether mild or severe, can markedly impair cognitive functioning (Boone et al. 1995). Persons with long-standing schizophrenia frequently develop severe cognitive impairment (Purohit et al. 1998). Cognitive impairment due to malingering occurs in individuals facing imprisonment (Allen et al. 2000), and fugue states may develop in individuals seeking to escape the consequences of acts such as bigamy. In Ganser syndrome, patients unconsciously provide answers that are incorrect (see description in Chapter 3, "Neuropsychiatric Assessment and Diagnosis").
5. *Does the individual have behavioral or psychiatric symptoms?* Frequently, the first symptoms noted in a dementing illness are loss of initiative and loss of interest in activities that were formerly pleasurable. Individuals with impaired frontal lobe function may show apathy and/or disinhibition. Suspiciousness and irritability may accompany early dementing illness, as may depression or elation and grandiosity. Depressive, psychotic, and obsessive-compulsive symptoms may herald the onset of Huntington disease (De Marchi and Mennella 2000). Visual hallucinations unaccompanied by explanatory delusions are frequent in

Alzheimer disease and dementia with Lewy bodies. Tactile hallucinations and illusions are common in delirium. Complex delusional systems are unusual in dementing illness. Auditory hallucinations in dementia tend to be of familiar others speaking or music playing, whereas accusatory or threatening voices that speak through the radio or television are more characteristic of schizophrenia. Sleepwalking and rapid eye movement (REM) sleep behavior disorder often precede the onset of synucleinopathies such as Parkinson disease and dementia with Lewy bodies (Ferman et al. 2004) (see also Chapter 11, "Dementia With Lewy Bodies and other Synucleinopathies").

6. *Does the individual have associated neurological symptoms?* Neurological symptoms often suggest specific dementia diagnoses. Such symptoms may include loss of consciousness, seizures, loss of coordination, gait and balance problems, movement disorders, weakness (generalized or localized), impairment of vision or hearing, and other cranial nerve dysfunction. Loss of consciousness may accompany severe head trauma, lupus cerebritis, and toxic-metabolic disorders. Seizures may point to a primary seizure disorder or to another condition such as neoplasm, in which seizures are secondary. Gait apraxia and early urinary incontinence are associated with normal pressure hydrocephalus. The combination of dysarthria and paralysis of gaze suggests progressive supranuclear palsy. Unilateral limb apraxia suggests corticobasal ganglionic degeneration (Schneider et al. 1996) or frontal dementia (Kertesz et al. 2001). Bradykinesia may indicate depression, early Parkinson disease, or another subcortical process. Lack of coordination and sensory and cranial nerve symptoms may indicate multiple sclerosis or progressive supranuclear palsy. Choreiform movements accompany Wilson and Huntington disease, whereas myoclonic jerks accompany Creutzfeldt-Jakob disease and mid- to late-stage Alzheimer disease (Chen et al. 1991). Lateralized abnormalities of strength, tone, reflexes, or sensation suggest a possible vascular origin. Visual field deficits point to possible vascular or neoplastic disease, and unilateral hearing loss raises a concern for possible neoplasm.
7. *Does the patient have a personal or family history of a disease or disorder associated with cognitive decline?* Diabetes, hypertension, strokes, hypercholesterolemia, heart disease, and/or signs of generalized atherosclerosis are risk factors for vascular dementia. Severe renal or hepatic disease may produce metabolic encephalopathy. Seropositivity for human immunodeficiency virus types 1 (HIV-1) raises the possibility of direct effects of the virus on the brain (HIV-1-associated minor cognitive motor disorder or HIV-1-associated dementia) (American Academy of Neurology AIDS Task Force 1991) or an opportunistic brain infection. Huntington disease and Wilson disease exemplify familial diseases associated with dementia. Alzheimer disease very rarely occurs as an autosomal dominant familial disease. Nearly half of frontal dementias may be hereditary (Chow et al. 1999; Knopman et al. 1990; Neary et al. 1988; Stevens et al. 1998; see "Genetic Markers" section later in this chapter).
8. *Does the person take any prescribed or unprescribed medications?* Medications that may impair cognitive function include anticholinergic drugs, benzodiazepine hypnotics and tranquilizers, barbiturates, anticonvulsants, propranolol, and cardiac glycosides. Episodes of confusion in persons with porphyria may be induced by various medications, including barbiturates and benzodiazepines (Sack 1990). In addition, patients and families should be asked specifically what sleep medications, over-the-counter medications (e.g., aspirin), vitamins, and other supplements (calcium, ginkgo biloba, St. John's wort, etc.) the patient is taking, as this information is often not proffered. Patients and their families should be asked in advance of the patient's appointment to bring in the patient's medication bottles and/or a detailed list including the name of each medication, its dose, and the number of times per day it is taken.
9. *Does the individual have a history of abuse or heavy intake of alcohol or other substances?* History of alcohol abuse may point to the origin of an amnestic disorder or dementia. Repeated episodes of delirium tremens are important. Substance abuse, such as glue or paint sniffing or crystal methamphetamine use, may cause cognitive impairment.
10. *Has the individual been exposed to environmental toxins?* Arsenic, mercury, lead, organic solvents, and organophosphate insecticides can produce encephalopathies, usually accompanied by severe systemic symptoms.
11. *Has the person been exposed to HIV infection?* Intravenous drug abuse and unprotected sexual contact are risk factors for infection with HIV in adults. Increased screening of blood and blood transfusions has virtually eliminated HIV transmission via transfusions. Highly active antiretroviral therapy has postponed the occurrence of AIDS caused by HIV as well as associated symptoms, such as AIDS dementia.

Even when the history suggests that a patient has a depressive disorder, is functioning normally, or is overreact-

ing to age-related cognitive changes, a formal mental status examination should be performed. When possible, information should be obtained separately from a knowledgeable informant. It is wise to obtain a baseline measure of cognitive performance such as the Mini-Mental State Examination (Folstein et al. 1975) or the more sensitive Montreal Cognitive Assessment (Nasreddine et al. 2005). Follow-up should also be arranged, with a revisit scheduled after a period of 1 year or sooner, depending on the findings of the initial evaluation and progression of any problems.

Physical Examination

A general physical examination is an important part of the medical evaluation. Diseases of many organ systems can lead to transient or progressive impairment of brain function or contribute to excessive morbidity in dementing illness.

Funduscopic examination may reveal optic atrophy in the case of multiple sclerosis or papilledema in the case of increased intracranial pressure such as tumor. Cardiovascular examination may demonstrate an irregular rhythm consistent with atrial fibrillation and increased risk for stroke. Carotid bruits may be an indicator of stenosis. Abdominal examination may reveal the presence of hepatomegaly. Examination of the skin and extremities may reveal signs of vasculitis such as petechiae.

Neurological Examination

A detailed neurological examination is performed on every patient (see Appendix D). The components of this examination and use of the data for diagnostic purposes are described in this section.

Cranial Nerves

Cranial nerve examination may include olfaction, but the relationship of olfactory deficits to dementing illness remains controversial. There is wide consensus that olfactory deficits occur in Alzheimer disease and Parkinson disease (Mesholam et al. 1998), but such deficits also occur in normal elders. Bacon et al. (1998) found changes in olfactory threshold in the year preceding change in diagnosis from nondemented to Alzheimer disease. On the other hand, a neuropathologically confirmed study showed no difference in olfactory discrimination between patients with Alzheimer disease and control subjects, but a significant difference between control subjects and subjects with cortical Lewy bodies (McShane et al. 2001). Anosmia of sudden onset may point to a significant head injury.

It is important to test visual and auditory acuity because sensory impairment may influence mental status testing. Pupillary abnormalities occur with neurosyphilis but may also result from cataract surgery. The typical Argyll Robertson pupil seen with neurosyphilis is small, irregular, and reactive to accommodation but not to light. Retinal examination may reveal damage from long-standing hypertension or diabetes. Impairment of gaze in progressive supranuclear palsy usually affects downward gaze first, then upward gaze, and finally horizontal gaze.

Asymmetry of the facial muscles in the lower part of the face occurs with an upper motor neuron lesion such as a stroke or tumor. Weakness of muscles (e.g., tongue, sternocleidomastoid, and trapezius) supplied by other cranial nerves and/or altered facial sensation may also suggest a stroke.

Motor System

Patients are assessed for muscle bulk, tone, and strength, as well as for any apraxia or abnormal involuntary movements, such as tremor, dyskinesia, or chorea. Increased resistance to passive movement (rigidity) is common as Alzheimer disease progresses. The occurrence of rigidity early in the course of a dementing illness may indicate a parkinsonian syndrome, especially when accompanied by tremor or other parkinsonian symptoms. Clonus may be demonstrable in patients with upper motor neuron damage due to a stroke or spinal damage. Myoclonus—a lightning-like jerk of a limb, limbs, or the entire body—may be induced by testing reflexes (reflex myoclonus) or if the patient is suddenly startled (startle reflex), such as by a loud noise. Myoclonus in the setting of rapidly progressive dementia should raise the possibility of Creutzfeldt-Jakob disease, but myoclonus may occur later in the course of other dementias, such as Alzheimer disease and Lewy body disease.

Parkinsonism

We prefer the term *parkinsonism* to the more nonspecific term *extrapyramidal symptoms*. Bradykinesia, resting tremor, rigidity, and postural instability are the cardinal signs of idiopathic Parkinson disease. The presence of two or more, but not all, of these signs suggests secondary parkinsonism, such as medication-induced parkinsonism and Parkinson-plus syndromes, such as Lewy body disease. Other parkinsonian features that may be seen in Parkinson disease and these related syndromes include restriction of extraocular movements, masklike facies, hypophonia, dysarthria, dysphagia, collapsing move-

ments, micrographia, stooped posture, slow gait, turning en bloc, festinating gait, and decreased arm swing with walking. Consideration should be given to other factors, especially in the elderly, such as muscle deconditioning and medications, which may cause or contribute to some of these symptoms.

Sensation

Vibration sense in the lower extremities is frequently reduced in the elderly, but position sense is not. Sensory neuropathies, characterized by loss of vibratory and pinprick sensation in the periphery, and greatest distally, occur in individuals with hypothyroidism, significant alcohol use, diabetes, syphilis, and vitamin B_{12} deficiency. In the case of the tabes dorsalis syndrome of neurosyphilis, the dorsal columns are involved, and both vibratory and position sense are frequently impaired due to involvement of the dorsal columns.

Reflexes

Deep tendon reflexes are generally reduced in a patient with sensory neuropathy. Increased deep tendon reflexes may accompany the sensory neuropathy of vitamin B_{12} deficiency. Asymmetric reflexes and the presence of a plantar extensor response (Babinski reflex) suggest upper motor neuron pathology. Frontal release signs, also called frontal reflexes or primitive reflexes (grasp, palmomental, rooting, snout, suck), may be seen even in healthy elderly persons. These signs are therefore relatively nonspecific, except when seen in younger adult patients and in the context of other frontal abnormalities on neurological or mental status examination.

Gait and Posture

Gait tends to slow with aging, and tandem walking may be difficult for elders. The gait of older persons, sometimes called the cautious or senile gait, often has a narrow or slightly wide base and a short stride length with en bloc turning. Gait apraxia, also called magnetic gait, in which a patient has difficulty initiating steps, raises the possibility of normal pressure hydrocephalus.

Classification of Dementias

Data from the neurological examination, mental status examination, and history enable the clinician to classify dementing illnesses into frontotemporal, temporoparietal, or subcortical types. The neurological examination facilitates the differentiation of dementing illness into these categories and the categories of cortical, subcortical, and mixed dementing illness. Frontotemporal disorders are often accompanied by cortical release signs such as the palmomental, suck, and snout reflexes; language impairment; perseveration; and disinhibition. Temporoparietal disorders, in addition to severe difficulty with recent memory, are often accompanied by difficulty with word finding and spatial orientation. Subcortical dementias may be accompanied by apathy, disinhibition, and emotional lability. These illnesses also tend to have motor signs that may be pyramidal or extrapyramidal. The anatomical loci for cortical dementias are the neocortical association areas and hippocampus; the loci for subcortical dementias are the thalamus, basal ganglia, and rostral brain stem (Albert et al. 1974). Based on the foregoing criteria, the prototypical cortical dementias are Alzheimer disease and frontotemporal dementia/Pick disease, but mild extrapyramidal signs, such as rigidity and bradykinesia, can occur in conjunction with Alzheimer disease. Typical subcortical dementias are Huntington disease, Wilson disease, AIDS dementia, and progressive supranuclear palsy. Vascular dementia, Creutzfeldt-Jakob disease, and trauma typically produce mixed cortical and subcortical signs.

Laboratory Studies

Blood

For clinical evaluation of dementia, the Quality Standards Subcommittee of the American Academy of Neurology (Knopman et al. 2001) recommended routine blood tests, including serum electrolytes; glucose, blood urea nitrogen/creatinine, folate, and vitamin B_{12} concentrations; and thyroid stimulating hormone level. Syphilis testing was recommended only for clinical suspicion of neurosyphilis.

Low-normal levels of vitamin B_{12} (<400 pg/mL) have been associated with neuropsychiatric symptoms, so levels in this range may indicate a need for supplementation, especially in an individual presenting with cognitive deficits. Methylmalonic acid may be checked to help determine whether supplementation is needed and whether folate should also be added, as levels are elevated in vitamin B_{12} deficiency but not folate deficiency. Patients with homocysteine levels above 15 μmol/L, low or low-normal B_{12}, or methylmalonic acid levels above 950 nmol/L can be treated with oral cobalamin supplements.

Hyperhomocysteinemia has been associated with stroke, dementia, depression, and Parkinson disease (Reutens and Sachdev 2002). Whether levels of homocysteine are risk factors or simply risk markers has not been

established (Seshadri 2006). Subjects treated with 2.5 mg of folic acid, 50 mg of vitamin B_6, and 1 mg of vitamin B_{12} had a reduced risk of stroke, but not of myocardial infarction or death from cardiovascular causes, compared with those on placebo (Wang et al. 2007). Assessment of plasma homocysteine level is a reasonable addition to laboratory studies of persons presenting with cognitive complaints.

A lipid profile is advisable because hypercholesterolemia is an independent and treatable risk factor for cerebrovascular disease.

Serum ceruloplasmin and 24-hour urinary copper are determined in possible cases of Wilson disease, as in a young person (age less than 40 years) presenting with cognitive impairment. It is also necessary to measure 24-hour urine copper output because serum ceruloplasmin may be low or normal in a person with Wilson disease.

If there is a suspicion of covert or unreported drug use or of exposure to toxins such as lead or mercury, appropriate toxicological testing may be performed. When indicated, serum levels of medications that produce confusion (including digitalis, anticonvulsants, and lithium) may be useful.

Urine

In the case of frail elders, a urinalysis is indicated routinely. A urinary tract infection will cause confusion (usually delirium) in some people, but others may present only with a worsening of cognitive state. Urine studies (see Table 4–2) may be indicated in individuals with suspected substance abuse, Wilson disease, porphyria, or exposure to heavy metals.

Spinal Fluid

No additional studies of the use of lumbar puncture for the evaluation of persons with cognitive impairment have been done since the review by Hammerstrom and Zimmer (1985), who concluded that lumbar puncture is not indicated routinely. Routine use of lumbar puncture is not included in the recommendations of the American Academy of Neurology (Knopman et al. 2001), but lumbar puncture is indicated specifically in rapidly progressive dementia, positive syphilis serology, and suspected central nervous system infection. It is also indicated in all cases of dementia occurring in persons with diagnosed or suspected AIDS and in persons who have had a blood transfusion. The detection of the 14-3-3 protein in cerebrospinal fluid is useful in confirming the diagnosis of Creutzfeldt-Jakob disease (Zerr et al. 1998), but a negative result does not exclude Creutzfeldt-Jakob disease. In the diagnosis of Alzheimer disease, measurements of amyloid $beta_{1-42}$, tau, or *AD7C-NTP* levels in cerebrospinal fluid have not been shown to increase diagnostic specificity and are not recommended for routine diagnosis (Knopman et al. 2001).

Special Diagnostic Procedures

Genetic Markers

No genetic markers are recommended for routine diagnostic purposes (Knopman et al. 2001) or for asymptomatic persons concerned about the future development of dementing illness (Post et al. 1997; Small et al. 1997). Genetic testing may be appropriate for some asymptomatic persons in selected cases of hereditary dementing illnesses such as Huntington disease, for which genetic testing can confirm a diagnosis of or detect presymptomatic disease (Research Group on Huntington's Chorea 1994). Mutations in the amyloid precursor protein gene and the presenilin 1 and 2 genes can be detected in some cases of familial early-onset Alzheimer disease (Rosenberg and Iannaccone 1995); all cases of Alzheimer disease with onset before age 35 years appear to have presenilin 1 mutations (Filley et al. 2007). Inheritance of the cholesterol-transporting protein apolipoprotein E is associated with late-onset familial and sporadic Alzheimer disease, but it cannot be used as a diagnostic test or to predict the onset of Alzheimer disease. It is therefore not recommended for asymptomatic persons. However, in persons who meet clinical criteria for Alzheimer disease, the presence of the apolipoprotein E ε4 allele increases the specificity of the diagnosis from 55% to 84% (Mayeux et al. 1998). Multiple genetic loci (on chromosomes 3p, 9p, 9q, 17q21, and 17q24) and four genes (microtubule-associated protein tau, progranulin, valosin-containing protein, and charged multivesicular body protein 2B) have been associated with inherited frontotemporal lobar degeneration (Bugiani 2007; Mackenzie and Rademakers 2007; Rademakers and Hutton 2007). To date, however, genetic testing for frontotemporal lobar degeneration is available only in research laboratories.

Neuroimaging

An extensive overview of neuroimaging is presented in Chapter 6. The American Academy of Neurology (Knopman et al. 2001) published a guideline recommendation for structural neuroimaging, brain magnetic resonance imaging (MRI), or computed tomography (CT) of the head for dementia diagnosis. Brain MRI is the structural neuroimaging test of choice. It is not necessary to perform brain MRI

with contrast medium, but gadolinium may be indicated for some patients, particularly if the history or examination raises concern for neoplasm or infection. In our experience, structural imaging rarely leads to the discovery of treatable causes for cognitive impairment in persons with slowly progressive cognitive impairment who have normal physical and neurological examinations. However, Figure 4–1 is a magnetic resonance image of a man in his late 70s whose only symptom was mildly impaired memory. His frontal lobe meningioma was later resected. Functional neuroimaging, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), may be employed in diagnostic dilemmas. PET has been approved by Medicare as a diagnostic procedure for differentiating frontotemporal dementias from Alzheimer disease.

Cisternogram

Radionuclide cisternography is used to differentiate communicating and noncommunicating hydrocephalus. It also helps establish the diagnosis of normal pressure hydrocephalus by demonstrating reflux into the ventricles and delayed pericerebral diffusion.

Other Diagnostic Procedures

Angiography

Intracerebral angiography should be performed for specific indications, such as diagnosis of aneurysms; vascular malformations; occluded arteries and veins; and mass lesions, such as hemorrhages, abscesses, and neoplasms. Contrast medium injected percutaneously into a carotid, brachial, or femoral artery allows visualization of the entire circulation of the neck and brain. Risks of this procedure include embolization, as well as arterial spasm and occlusion.

Magnetic resonance angiography and CT angiography, which produce computer-generated images of the major cervical and intracranial arteries, are much more benign and less expensive techniques but are somewhat less precise. These techniques involve the intravenous injection of a small amount of contrast material.

Carotid and Transcranial Sonography

Evidence of generalized arteriosclerosis, carotid bruits, transient ischemic attacks, or stroke warrants sonographic investigation of the carotid and intracranial vasculature. Patients with evidence of stroke on history, examination, or neuroimaging are referred for echocardiography to be evaluated for any cardiac source of emboli. Patients with evidence of large-vessel cerebrovascular disease are referred for cerebral angiography. Transcranial Doppler imaging may be performed to image the intracranial vasculature, including the circle of Willis (Sadik et al. 2001).

Electroencephalography

The electroencephalogram is of limited value in the evaluation of cognitive impairment. It has been argued that electroencephalographic (EEG) evidence of abnormal brain function is useful in distinguishing between a degenerative disease and a psychiatric disorder, such as depression (Brenner 1999). In practice, however, the sensitivity and specificity of electroencephalography is low. EEG findings in Alzheimer disease include slowing of the posterior dominant rhythm, an increase in diffuse slow (theta or delta) activity, and generalized bursts of slow activity, but none of these findings is specific or sensitive for Alzheimer disease. Most persons with severe to moderate Alzheimer disease have such EEG abnormalities, reflecting the degree of impairment of cortical function. However, the electroencephalogram is often normal early in the illness (Markand 1990).

Most persons with frontotemporal dementia/Pick disease have normal electroencephalograms (Stigsby 1988). Huntington disease patients typically show low voltage (Robinson et al. 1994), but this pattern is neither sensitive nor specific. The presence of triphasic waves frequently indicates a delirium due to toxic or metabolic disorders (Engel and Romano 1959).

Electroencephalography can be useful in the diagnosis of patients with rapidly progressive cognitive deterioration in whom Creutzfeldt-Jakob disease is considered in the differential. In persons with Creutzfeldt-Jakob disease, the EEG pattern is distinctive. In the initial phase of the illness, EEG changes consist of a progressive disorganization of background rhythms and increased amounts of generalized slow (theta-delta) activity. As the disease progresses, the electroencephalogram is characterized by periodic, bilaterally synchronous, sharply contoured biphasic and triphasic waves, which appear at irregular intervals of one or two per second (Brenner 1999). These findings have a sensitivity of 67% and a specificity of 86% compared with neuropathological findings in prospectively studied patients in whom Creutzfeldt-Jakob disease was clinically suspected (Steinhoff et al. 1996). Similar EEG findings have been reported in rare cases of lithium intoxication, baclofen encephalopathy, myoencephalopathy ragged–red fiber disease, and HIV encephalopathy (Brenner 1999).

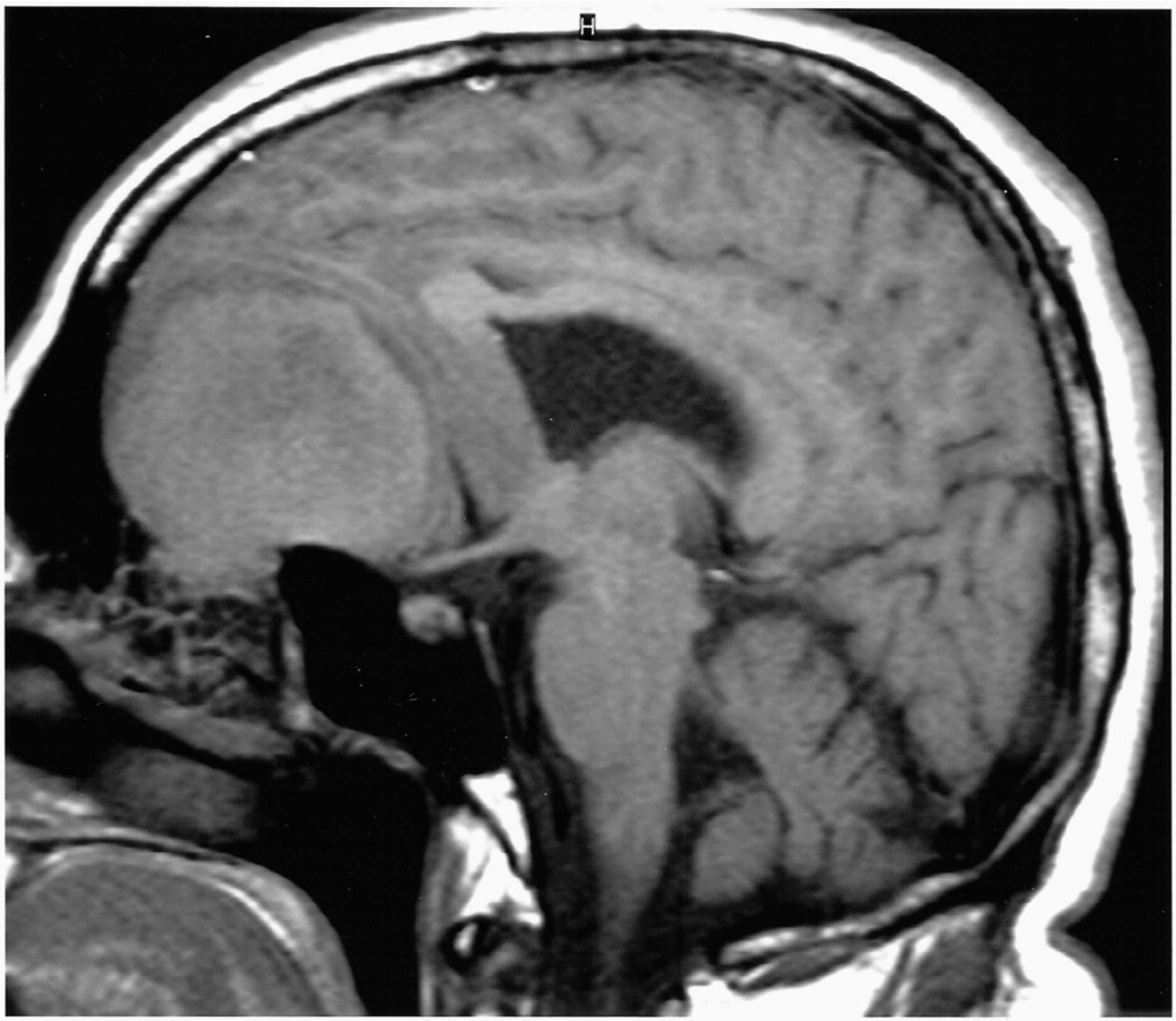

FIGURE 4–1. Frontal lobe meningioma in an elderly man with mild memory loss as presenting complaint.

EEG studies are most widely performed in the evaluation of cognitively impaired persons who appear to have epileptic seizures. Several studies indicate that epilepsy complicates 5%–25% of cases of Alzheimer disease (Risse et al. 1990); Amatniek et al. (2006) found an 8% cumulative incidence of seizures in patients with Alzheimer disease over 7 years. The diagnosis of Alzheimer disease or other dementia increases the risk of unprovoked seizures approximately sixfold (Hesdorffer et al. 1996). However, persons with dementing illness are also at high risk for other paroxysmal events that mimic epileptic seizures, including transient ischemic attacks, syncopal episodes, and acute behavioral disturbances. Electroencephalography is often the best way to establish the diagnosis, because the presence of paroxysmal generalized or focal spikes, sharp waves, or sharp and slow wave complexes (interictal epileptiform discharges) are highly predictive of epileptic seizures. Although the specificity of interictal epileptiform discharges for epileptic seizures is high (>95%), the sensitivity in elderly patients is poor (25%–35% for patients age 65 years or older, compared with 50%–70% for younger persons (Drury and Beydoun 1998).

Quantitative electroencephalography and long-latency cortical evoked potentials such as the P300 do not seem to add to clinical diagnostic specificity in the dementing illnesses, although they remain a subject for clinical research. Neither technique is mentioned in recently published practice parameters for the diagnosis of dementia in the United States (Knopman et al. 2001) or Europe (Waldemar et al. 2007).

Brain Biopsy

Brain biopsy is reserved for situations in which a treatable illness is suspected. We have reserved this procedure for suspected autoimmune cerebral vascular disease and infectious brain diseases not diagnosable by spinal fluid studies. Brain biopsy is of limited use in that only small amounts of tissue can be sampled, and the brain areas most affected by diseases such as Alzheimer disease are not readily accessible. Brain biopsy is generally not advisable in cases of suspected Creutzfeldt-Jakob disease because of the possibility of transmission to others and the untreatable nature of this illness.

Extent of Evaluations

Opinions differ as to what is an adequate laboratory workup for dementing illness. The Canadian guidelines (Mohr et al. 1995) suggest that the following tests be performed only if indicated by history or physical examination: tests for blood urea nitrogen, vitamin B_{12}, and folic acid levels; serologic test for syphilis; urinalysis; and erythrocyte sedimentation rate screening. The guidelines also suggest neuroimaging only if patients are younger than age 60 years; use anticoagulants or have a history of bleeding disorder; have experienced recent head trauma; or have cancers that metastasize to the brain, unexplained neurological symptoms, rapid progress of disease, dementia duration of less than 2 years, or urinary incontinence and gait disorder suggestive of normal pressure hydrocephalus (NPH). As noted above, the Quality Standards Subcommittee of the American Academy of Neurology (Knopman et al. 2001) recommends routine blood tests to assess serum electrolytes, glucose, blood urea nitrogen, creatinine, folate, vitamin B_{12}, and thyroid function. The European Federation of Neurological Societies guidelines (Waldemar et al. 2007) are similar except they do not include blood urea nitrogen, creatinine, or vitamin B_{12} levels on a routine basis. Syphilis serology is recommended only if there is clinical suspicion of neurosyphilis. Structural neuroimaging with CT or MRI is now a guideline recommendation of the American Academy of Neurology (Knopman et al. 2001).

A minimum medical workup for dementia includes a history (with careful scrutiny of medications), physical and neurological examination, mental status examination, brain MRI (preferably) or CT of the head, and some laboratory studies. Routine laboratories, such as complete blood count and differential, lipid profile, electrolytes, urea nitrogen, creatinine, and blood glucose, are helpful in identifying underlying medical conditions. Laboratory workup for dementia often includes thyroid stimulating hormone, vitamin B_{12}, folate, homocysteine, and serologic tests for syphilis. Erythrocyte sedimentation rate, calcium, magnesium, and liver function tests may be indicated in some cases. Lumbar puncture is indicated if an infectious, inflammatory, or autoimmune disorder is suspected. EEG should be ordered if epilepsy or Creutzfeldt-Jakob disease is suspected. Functional neuroimaging is important for the differential diagnosis of atypical dementias.

Frequency of Evaluations

Brief reevaluations, including an interim clinical history, a neurological examination, and mental status testing, should be performed at least yearly. Monitoring progression of the illness through history and examination and by noting the response to any treatment may help to confirm the original diagnosis or raise doubt if the typical clinical course and findings are not observed. An unusually fast progression may raise suspicion for an illness such as Creutzfeldt-Jakob disease. Marked improvement may suggest that a reversible disease, even depression, is responding to treatment or remitting. New focal signs may point to a vascular or neoplastic component. More comprehensive evaluations are indicated when such new findings arise, particularly when a reversible component of cognitive impairment is suspected.

Additional comprehensive evaluations are not indicated when an adequately diagnosed disease process is following its predicted course. A minimum evaluation in these cases includes a medication check and a medical examination, including brief mental status testing.

Conclusion

Although differences exist as to the exact procedures used to determine the etiology of cognitive impairment or dementing illness, the medical evaluation of cognitive impairment requires accurate history taking, mental status examination, physical and neurological evaluation, a relatively small number of blood tests, and neuroimaging. Illnesses that progress rapidly or that have an atypical course warrant more comprehensive investigation at a tertiary care center, where investigators have experience with a variety of dementing illnesses. As techniques and treatments evolve, methods such as functional neuroimaging may be used more frequently as a means for early detection and monitoring the course of treatment.

KEY POINTS

- The sudden worsening of cognitive impairment or behavior in a person diagnosed with dementia, subjective complaints of cognitive impairment, or the objective development of cognitive impairment should suggest further clinical assessment.
- Potential identification of a reversible dementia etiology is an important reason for clinical evaluation.
- An acute onset suggests delirium rather than dementia.
- Recommended tests for dementia are serum electrolytes; glucose, blood urea nitrogen/creatinine, folate, and vitamin B_{12} concentrations; and thyroid-stimulating hormone level.
- Structural neuroimaging is recommended for evaluation of suspected dementing illness.
- Genetic testing is generally not necessary or indicated in clinical evaluation of dementia.

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CHAPTER 5

Neuropsychological Assessment in Dementia

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Neuropsychological evaluation is an important component of the comprehensive neurodiagnostic workup. In addition to lending a quantitative aspect to characterizing a person's level of dementia and cognitive functioning, neuropsychological assessment provides information regarding specific cognitive strengths and weaknesses and allows for comparison of cognitive patterns across disorders, thereby assisting with differential diagnosis. Serial neuropsychological examinations extend the utility of baseline or diagnostic cognitive assessment by providing data used to track areas of cognitive change over time, chart the rate of progression, plan treatment, and make recommendations for behavioral and environmental adaptations. Neuropsychological testing is an accepted medical diagnostic procedure (Current Procedural Terminology codes 96118 to 96120) (American Medical Association 2006), and one of the primary indications for neurocognitive evaluation is dementia (Therapeutics and Technology Assessment Subcommittee 1996).

The neuropsychological evaluation includes the administration of standardized neurocognitive tests. Such measures reflect behavioral samples of cognitive function that tap various brain-related abilities and, indirectly, their underlying neural systems. Test development relies on principles from psychology, neurology, neuroscience, and related fields. Most current measures involve pencil-and-paper and question-answer types of tasks, whereas others include manipulation of various test stimuli and may involve computer-based tasks. Neuropsychological tests are carefully developed, with highly standardized instructions and scoring criteria. Rigorous standardization and sound psychometric properties are hallmarks of neuropsychological testing.

Neuropsychologists have developed an ever-growing array of clinical and experimental measures of cognitive functioning. Some of the more popular tools in clinical use are summarized in Lezak et al. (2004) and Strauss et al. (2006). The tests vary in terms of design, content, goals, rigor of standardization, and availability of normative ref-

erence data, but the tools in general clinical use have demonstrated validity and reliability, and research and practice have determined their clinical utility. No single neuropsychological test can be used for all purposes, and no universal test battery is ideal for all patients or addresses all referral questions. Most neuropsychologists select tests based on their own training and experience, taking into account the patient's background, presenting complaints, and possible diagnoses, as well as the referral question(s) (see Table 5–1). Test batteries are typically tailored to the referral question, although a common core group of measures may be administered to most persons with known or suspected dementia.

TABLE 5–1. Neuropsychological test selection considerations

Sensitivity for purpose (determining presence or absence of impairment; documenting level of impairment)
Efficiency (minimizing time and cost to answer referral question, particularly when issues of patient fatigue and tolerance are present)
Appropriateness of cognitive screening (limited time; need to identify patients who need more comprehensive assessment)
Availability of alternate forms (when test-retest is needed)
Availability of appropriate and adequate norms (age, ethnicity, and cultural factors)

Neurocognitive Assessment in the Diagnosis of Dementia

U.S. census figures indicate that the oldest segment of our population is the fastest growing (U.S. Census Bureau 2004); therefore, it is essential for clinicians to be familiar with the cognitive changes that typically accompany normal aging. Changes in intellectual and several other cognitive abilities do not become apparent until the eighth decade for many persons. Table 5–2 lists some of the most commonly reported areas of cognitive change associated with normal aging, with reduced mental processing speed being the most common and consistent, often beginning after the fifth decade of life (Smith and Rush 2006).

TABLE 5–2. Cognitive declines associated with aging

- Mental speed of processing
- New learning/Episodic memory
- Recall of details
- Executive functioning
- Visuospatial functioning
- Word-finding ability

Many genetic and environmental factors play a role in the cognitive changes each person experiences with aging, and there is wide variability across individuals. Factors such as overall physical health and higher or ongoing education have been associated with greater retention of intellectual abilities later in life (Friedland 1993; Heaton et al. 1986), although the great variability that exists among older adults prevents clinicians from being able to predict who will and will not age "gracefully" from a cognitive perspective. Memory decline associated with aging has been described using various terms (e.g., see Smith and Rush 2006), although acceptance of and criteria for such terms are not uniform. The high degree of individual variability in memory functions among elderly individuals contributes to a wide range of what is considered normal cognitive aging.

Before selecting individuals for normative comparison groups for cognitive test results, test authors and publishers must decide on and operationally define what constitutes "normal" for inclusion in the sample. They need to consider, for example, whether it is normal to reach age 90 years without experiencing a major medical illness or having central nervous system risk factors such as vascular disease. Because normative samples vary in age and other demographic characteristics, caution is sometimes needed when comparing scores across different measures. For example, in the Mayo's Older Americans Normative Studies (MOANS; Ivnik et al. 1992), researchers have compiled normative data for many frequently used neuropsychological measures with large numbers of older adults, for whom the researchers also have follow-up data to provide information on expected changes in normal aging across measures. In general, few cognitive functions remain stable with aging, although crystallized verbal abilities, such as vocabulary skills and sight-word reading, do not deteriorate much with age and thus are often used in helping to determine long-standing or premorbid intellectual abilities.

Detailed assessment of cognitive changes in an individual patient offers the best opportunity for discriminating age-related from disease-related changes in cognitive status (Albert and Moss 1988), and the neuropsychological evaluation remains the most sensitive means of assessing human cognitive function. An individual's performance on neuropsychological tests is combined with

TABLE 5–3. Sources of information for the neuropsychological examination

- Referral question and related information
- Review of patient's history
- Interview with patient
- Collateral information from informants (e.g., relatives familiar with patient)
- Neuropsychological testing of a range of neurocognitive skills and domains

historical, developmental, educational, and medical information to assist in diagnosis. Background demographic factors such as age, education, and sociodemographic status must be taken into account, because these factors are usually related to performance on cognitive tests. For example, low performance on a cognitive test by an individual with limited premorbid intelligence and education may not be due to a decline in functioning. Conversely, an average performance on cognitive tasks by someone with an advanced degree may represent early cognitive decline. Hence, *level* of performance alone may not be adequate to diagnose dementia; the *pattern* of performances across tests is important as well.

Comprehensive Neuropsychological Evaluation for Dementia

The comprehensive neuropsychological evaluation assesses multiple cognitive domains and abilities and interprets them within the framework of an individual's life context. This requires an integration of information from multiple sources, including those listed in Table 5–3.

The Referral Question

The referral question is very important in helping to characterize the nature of the patient's primary presenting complaints, as well as in guiding the plan for test selection and crafting the summary and recommendations in the neuropsychological report. Different groups of tests would be used depending on whether the primary purpose of the examination is to assist with differential diagnosis or simply to document level of cognitive impairment. Also, less extensive testing is needed for a patient who has a history of dementia than for a patient who is referred for occasional memory problems at work. Table 5–4 lists some of the clinical issues for which neuropsychological testing can be helpful as an adjunctive neurodiagnostic procedure, and Table 5–5 lists factors that may make referral questions difficult to address from a neuropsychological perspective.

TABLE 5–4. Typical clinical issues addressed by neuropsychology

- Detecting subtle deficits (particularly in high-functioning individuals)
- Aiding in differential diagnosis of dementia
- Characterizing cognitive strengths and weaknesses (helping identify and develop appropriate compensatory strategies)
- Characterizing pattern of function (localization, lateralization, multifocal, diffuse)
- Assisting in designing intervention strategies to help optimize patient functioning
- Quantifying pre- and postintervention changes (e.g., medication trial, neurosurgical intervention)
- Identifying and assessing impact of psychiatric factors
- Determining need for rehabilitation services
- Determining ability to return to work or school
- Assisting with disability determination and/or need for placement
- Aiding in clinical decision making and recommendations to patients (e.g., issues regarding driving, safely living alone, making independent judgments, need for placement)

Length and Cost of the Neuropsychological Examination

Neuropsychological evaluations vary in length, depending on many factors, including the referral question and the patient's background (i.e., age and education) and level of functioning. Brief screening batteries may be used to detect or rule out severe cognitive impairment, but more detailed examinations are typically needed to address differential diagnostic issues and assist with recommendations for everyday living. Some neuropsychological evaluations may take less than an hour, but most routine

TABLE 5–5. Complicating factors in neuropsychological testing

- Medically unstable patient
- Acute or severely psychotic patient
- Profound cognitive compromise
- Precise prediction of clinical course

examinations of persons with suspected dementia require several hours of testing, in addition to a clinical interview and the time spent selecting and interpreting the tests. Neuropsychological tests may be administered by a clinical neuropsychologist or by a trained psychometrist under the neuropsychologist's supervision. Neuropsychological evaluations are covered at least in part by most medical insurance plans, although regional practices and coverages vary widely.

Neuropsychological Testing of Elders

Although many neuropsychological tests are sensitive to dementia, some are more appropriate than others for use with elders and individuals with known cognitive impairment. A number of brief cognitive screening measures and test batteries have been developed specifically for patients with dementia, and a variety of brief cognitive screening measures are commonly used in standardized mental status examinations and in large-scale research studies. Table 5–6 lists some of the advantages of formal neuropsychological testing over bedside mental status testing.

Neuropsychological Evaluation of Cognitive Domains

Global cognitive status is typically assessed by screening tools that include several different types of cognitive tasks or items that are summed to yield a global score indicating level of impairment. Representative dementia screening tests are described in Table 5–7.

Brief cognitive screening tasks are commonly used to examine the effects of medications on overall cognitive status and in clinical and research settings to provide a quick index of level of overall dementia severity. Such

TABLE 5–6. Advantages of neuropsychometric testing over mental status testing

- Standardized administration and scoring
- Documented validity and reliability
- Enhanced sensitivity and specificity
- Availability of normative data

Source. Adapted from Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology 1996.

tools are limited, particularly when used in isolation, because of their brevity and insensitivity to subtle cognitive impairments (see Table 5–8).

To illustrate the point that scores in the normal range on cognitive screening tests do not necessarily rule out dementia or cognitive impairment, we reviewed Mini-Mental State Examination (MMSE; Folstein et al. 1975) scores from a series of 673 subjects seen in the Alzheimer's Disease Center at University of Texas Southwestern Medical Center who had a clinical diagnosis of Alzheimer disease. Approximately 15% of this large sample obtained MMSE scores in the normal range (>23) (Cullum and Rosenberg 1998). If this type of study were performed outside of an Alzheimer disease center, we anticipate that the false-negative diagnoses based on MMSE scores alone would be significantly higher, given the lower base rates of dementia in general practice. Furthermore, variations in test administration (e.g., use of cues during memory tasks, liberal scoring) make such instruments more susceptible to variability due to factors aside from brain function. As with other neurocognitive measures, these tasks are influenced by factors such as age, education, and ethnicity; therefore, careful and use of appropriate norms are important in the interpretation of findings. For example, Figure 5–1 illustrates differences in three-word recall performance in two elderly samples (mean ages=70 vs. 81 years); corresponding normative data can be found in Table 5–9.

When bedside examination or cognitive screening yields suspect findings, or when detailed information regarding cognitive status is desired, formal neuropsychological evaluation is in order. Cognitive screening tasks are often included in the neuropsychological evaluation of dementia as well; this is done to provide a brief assessment of overall cognitive status at the outset of the examination so as to tailor the remainder of the test battery, to provide a standard score representing the patient's global status to facilitate quick comparisons with future screening data, and to enable ready communication regarding level of impairment.

Table 5–10 presents the cognitive domains typically assessed and included in the formal neuropsychological

TABLE 5–7. Common dementia screening tests

Mini-Mental State Examination (Folstein et al. 1975)
Available from Psychological Assessment Resources (http://www.minimental.com)
Time: 5–10 minutes
Most widely used cognitive screening test, available in multiple languages; various modified versions are available
Age- and education-adjusted norms (Crum et al. 1993; Folstein et al. 1975)
Scoring: 30 total points (orientation, language, attention, three-word recall, visuoconstruction); <24 suggests impairment (<27 in higher-functioning populations)
Three-word recall plus orientation items most sensitive to dementia

Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005)
Forms available at http://www.mocatest.org
Time: 10–15 minutes
Available in multiple languages
Limited norms available to date
Items: Trails, cube copy, clock draw, naming, five-item word list, digit span, repetition, verbal fluency, similarities, orientation
Scoring: 30 points total

Mini-Cog (Borson et al. 2000)
Time: 3 minutes
Items: three-word recall,clock drawing
Scoring: 3 points for words, 2 points for clock
Positive screen: Score of 0, or score of 1 or 2 with an abnormal clock
Negative screen: Score of 1 or 2 with normal clock, or score of 3

Alzheimer's Disease Assessment Scale—Cognitive (Rosen et al. 1984)
Time: 35–45 minutes
Widely used in clinical trials
11 cognitive items assessing memory, orientation, language, and praxis
Scoring: 21 items; total score range = 0–70

Memory Impairment Screen (Buschke et al. 1999)
Four-word learning with delayed free recall + category cues
Scoring=[2 x (free recall)] + [cued recall]
Scoring: ≤4 suggests dementia, depending on base rate in population
Normative tables and cut scores included in the article

General Practitioner Assessment of Cognition (Brodaty et al. 2004)
Brief cognitive screen for use in general practice
Time: 10 minutes
Patient Scale (maximum score=9): time orientation, clock drawing, reporting a recent event, word recall
Informant Scale (maximum score=6): memory for recent conversations, misplacing objects, word-finding difficulties, ability to manage money, need for travel assistance
Patient score of 5–8 indicates informant version should be done
Patient score of <5 or Informant score of <4 suggests cognitive impairment

Six-Item Screener (Callahan et al. 2002)
Time: 2–3 minutes
Items: Year, month, day of week, three-word recall
Score: <5 suggests impairment

The Dementia Rating Scale—2 (Jurica et al. 2002)
Available from Psychological Assessment Resources
Time: 30–40 minutes
A more detailed screening instrument than those listed above
Total Score (144 possible points) is summed from the following subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory
Scoring: 135–144=normal; 125–134=mild; 115–124=mild to moderate; 105–114=moderate; 95–104=moderate to severe; <95=severe

TABLE 5–8. Limitations of cognitive screening

- Heavily language-oriented content
- Limited assessment of visuospatial abilities
- Very brief (and possibly unreliable) memory items
- Lack of tests of executive function
- Insensitivity to subtle deficits
- Limited specificity
- Resulting "normal" score that does not rule out cognitive dysfunction

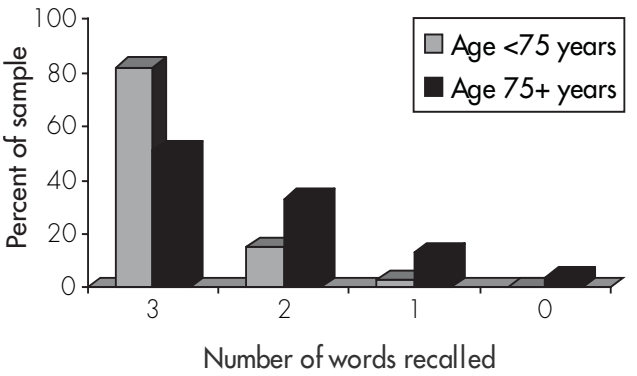

FIGURE 5–1. Three-word recall performance.
Percentage of healthy subjects ages <75 and ≥75 years correctly recalling 3/3, 2/3, 1/3, and 0/3 words.
Source. Adapted from Chandler et al. 2004.

report. Many neuropsychological tests have been developed to assess these various ability areas, including standard clinical measures and even more tests developed for neuroimaging and other cognitive neuroscience research questions. Table 5–11 lists some of the more commonly used clinical neuropsychological measures within each cognitive domain.

Intellectual Status

Obtaining an estimate of an individual's overall intellectual level is typically one goal of the comprehensive cognitive workup for dementia for several reasons. An estimate of global cognitive or intellectual status can be used to help determine the extent to which current intellectual results reflect a decline from presumed premorbid abilities. In addition, having an estimate of overall intellectual ability is useful in interpreting the results from other neurocognitive measures (i.e., determining whether memory test results are lower than expected given an individual's intellectual level). Because intellectual assessment tools generally comprise multiple subtests, the pattern of subtest scores can be useful for inferring cognitive decline in addition to providing information relevant to specific cognitive strengths and weaknesses. For example, a person's ability to define words tends to remain intact well into the course of dementia, although the ability to interpret proverbs or assemble three-dimensional blocks to replicate patterns may be impaired early on.

The Wechsler scales, including the Wechsler Adult Intelligence Scale, now in its fourth edition (WAIS-IV; Wechsler 2009), and its predecessors the WAIS-III (Wechsler 1997a) and WAIS-R (Wechsler 1981), are the most popular means to assess adult intellectual capacity. These scales are among the best standardized tests in clinical use; the norms are based on large representative samples of the general population. They evaluate academically acquired knowledge, in addition to many global verbal and visual-motor problem-solving skills important in daily life. Verbal and nonverbal intellectual abilities are assessed, and even though the utility of intelligence quotient (IQ) scores per se may be limited, composite scores can be derived that provide general descriptors regarding overall intellectual or cognitive capacity. The WAIS-IV and WAIS-III include a Verbal Comprehension Index and Perceptual Organization Index, which reflect global verbal and nonverbal cognitive skills. Although these measures may suggest a decline in intelligence, they are not sufficient to diagnose dementia, because many other areas of cognitive functioning are not assessed by these measures.

Although administration of an entire intellectual assessment battery may go beyond the scope of the typical dementia evaluation, some estimate of global intellectual level can be very useful in interpreting other neuropsychological results from patients with known or suspected dementia. Accordingly, a variety of short forms of standard intellectual tests have been developed, including the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation 1999), which has two- and four-subtest options in which the subtests are similar to those from the WAIS but include none of the same items. Other means of arriving at an estimate of global intelligence include administering several subtests of the Wechsler scales and using published formulas and tables for estimating IQ. For example, Ringe et al. (2002) examined various two-subtest short forms of the WAIS-III and found that using the Vocabulary + Block Design or Information + Matrix Reasoning subtest dyads resulted in adequate estimates of Full Scale IQ in a heterogeneous clinical sample. These estimated IQ scores correlated highly ($r \geq 90$) with Full Scale IQ. However, caution should be used when individual scaled scores are highly variable, because estimated IQ scores are likely to be less reliable in such cases.

TABLE 5–9. *T* scores for three-word recall using the words *apple*, *table*, and *penny* in normal aging

	Age (years)				
Words recalled	62–72 (*n*=42)	68–77 (*n*=65)	72–82 (*n*=83)	77–87 (*n*=63)	82–92 (*n*=35)
0	<1	4	12	20	27
1	12	21	27	33	38
2	33	38	42	46	48
3	54	55	57	59	59
M	2.79	2.69	2.55	2.33	2.17
(*SD*)	(0.47)	(0.58)	(0.67)	(0.78)	(0.95)

Note. Use age range in which midpoint best corresponds to age of patient. M = mean; SD = standard deviation.
Source. Adapted from Chandler et al. 2004.

TABLE 5–10. Cognitive domains assessed in neuropsychological evaluation

- Global functioning
- Estimation of premorbid level of function and current intellectual status
- Executive function
- Attention and concentration
- Language
- Visuospatial function
- Learning and memory
- Psychomotor function

Attention and Processing Speed

The capacity to attend to salient environmental stimuli is a prerequisite for adaptive behavior in all higher organisms. In humans, attention and concentration underlie higher neuropsychological processes. Attention reflects a complex array of activities involving the reticular, thalamic, and frontal systems of the brain (Wilkins et al. 1987). As cognitive processes become impaired, the fine-tuned balance between vigilance to novel stimuli and the focus on relevant stimuli is frequently disrupted. Thus, impaired selective attention in dementia patients may lead them to be either distractible or excessively focused. Accompanying problems in sustaining or dividing attention are also usually present (Butters et al. 1987; Lines et al. 1991).

Attention may be assessed in numerous ways. Simple attention can be assessed by tasks such as digit span forward, which does not require mental manipulation of information. Patients must have intact basic attentional skills to focus well enough to get through a mental status examination or any neuropsychological test. Sustained attention may be evaluated through requiring patients to be vigilant for recurrent target stimuli in a long auditory or visual sequence. Divided attention or sequencing tasks may require patients to alternate responding on a number-letter sequencing test (i.e., Trail Making Test).

Because attention is ordered hierarchically, patients with mild impairment may demonstrate little difficulty with simple or sustained attention even though they may have difficulty alternating their attentional focus. Those with more severe impairment will often have difficulty with all levels of attentional processing beyond the most basic of tasks. Thus, if impairment is seen at a lower level of attention (e.g., on the digit span forward task), deficits in higher-order attentional skills will be present and should be factored into the evaluation plan, as well as into the interpretation of other test results. If a patient fails to attend adequately to memory test stimuli at the encoding stage, delayed recall of that material cannot be validly tested.

Executive Function

Loss of executive processing abilities, such as organizing, planning, and evaluating one's own problem-solving behavior, is common in dementing illnesses. Executive functions are primarily mediated by frontal brain systems. Because this set of abilities represents the highest level of cognitive control and planning, executive functions rely heavily on a variety of supportive cognitive skills. Difficulties with planning, reasoning, and inhibition may manifest in many ways, and accurate assessment of this complex set of skills has proven challenging. Most commonly, these abilities are measured by neuropsychological tasks that rely heavily on novel problem-solving skills, such as the Wisconsin Card Sorting Test (Heaton 1981). The Delis-Kaplan Executive Function System (D-KEFS; Delis et

TABLE 5–11. Commonly used neuropsychological tests, by domain

Assessments	References
Global cognitive status	
Dementia Rating Scale–2	Jurica et al. 2002
Mini-Mental State Examination	Folstein et al. 1975
Montreal Cognitive Assessment	Nasreddine et al. 2005
Intellectual ability	
Selected subtests from WAIS-III[a] or WAIS-IV	Wechsler 1997a, 2008
Premorbid intellectual level estimation	
National Adult Reading Test—Second Edition	Nelson and Willison 1991
Wide Range Achievement Test—3, Reading subtest	Wilkinson 1993
Wechsler Test of Adult Reading	Psychological Corporation 2001
Attention and processing speed	
Digit span subtest (WAIS-IV, WAIS-III, or RBANS)	Army Individual Test Battery 1944; Randolph 1998; Wechsler 1997a, 2008
Trail Making Test, Part A	Army Individual Test Battery 1944
Digit Symbol-Coding subtest (WAIS-IV, WAIS-III)	Wechsler 1997a, 2008
Executive function	
Wisconsin Card Sorting Test	Heaton 1981
Trail Making Test, Part B	Army Individual Test Battery 1944
Stroop Interference Test	Spreen and Strauss 1991
Delis-Kaplan Executive Function System	Delis et al. 2001
Learning and memory	
Verbal learning and memory	
California Verbal Learning Test (CVLT, CVLT-II)	Delis et al. 1987; Delis et al. 2000
Hopkins Verbal Learning Test—Revised	Benedict et al. 1998
Rey Auditory Verbal Learning Test	Strauss et al. 2006
Logical Memory subtest (WMS-IV, WMS-III, WMS-R)	Wechsler 1987, 1997b, 2009
Nonverbal memory	
Visual Reproduction subtest (WMS-IV, WMS-III, WMS-R)	Wechsler 1987, 1997b, 2009
Rey-Osterrieth Complex Figure, Immediate and Delayed Recall	Corwin and Bylsma 1993
Visuospatial functioning	
Block Design subtest (WAIS-IV, WAIS-III)	Wechsler 1997a, 2008
Clock drawing	Goodglass and Kaplan 1983; Freedman et al. 1994
Rey-Osterrieth Complex Figure, Copy	Corwin and Bylsma 1993
Language	
Boston Naming Test (60-, 30-, and 15-item versions)	Kaplan et al. 1983; Lansing et al. 1999
Verbal fluency (letter fluency [FAS, CFL] and category fluency [animals, fruits])	Spreen and Benton 1977
Vocabulary subtest (WAIS-IV, WAIS-III)	Wechsler 1997a, 2008
Boston Diagnostic Aphasia Examination—Third Edition	Goodglass et al. 2001
Multilingual Aphasia Examination—Third Edition	Benton et al. 1994
Motor abilities	
Finger tapping test	Reitan 1969

Note. RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-III=Wechsler Adult Intelligence Scale—III; WAIS-IV=Wechsler Adult Intelligence Scale—IV; WMS-R=Wechsler Memory Scale—Revised; WMS-III=Wechsler Memory Scale—III; WMS-IV=Wechsler Memory Scale—IV.

[a]Selected WAIS-III or WAIS-IV subtests (e.g., Vocabulary or Information + Block Design or Matrix Reasoning) are often used to provide an estimate of current intellectual status.

al. 2001) is a well-normed battery of nine measures containing a variety of tasks that require set shifting, planning, and higher-order abilities.

Other tasks that rely on inhibition and the switching of mental sets (e.g., Trail Making Test, Part B; Stroop Test; go/no-go tasks) are also used in the evaluation of patients with cognitive complaints. Cognitive screening measures and bedside mental status examinations are notoriously poor at elucidating executive function impairments, and a history of clear executive function-related problem behaviors may be needed to make inferences in the absence of more detailed testing.

Memory

Memory difficulties are the most common problems reported by persons with dementing illnesses, depressed individuals, and healthy elderly. The clinician attempts to determine whether a patient's memory problem is due to a neuropathological process, medical illness, psychiatric disturbance, situational factor, or medication-related factor, or is a normal variation. Memory is a higher-order collection of mental processes that includes the collection, storage, and retrieval of information; it represents the integration of multiple functional brain systems (Squire 1992). Many different terms are used to describe memory functions (see also Chapter 3 of this volume, "Neuropsychiatric Assessment and Diagnosis"). For example, some clinicians classify memory as *immediate*, *recent*, or *remote*; others refer to immediate memory as short-term or *primary memory*, recent memory as long-term or *secondary memory*, and remote memory as *tertiary memory*. Sometimes the use of different terms to describe similar "memory" processes can be confusing, and clinicians are encouraged to use the most concrete, descriptive terms.

Memory involves a number of sequential cognitive processes. Information initially enters sensory memory, a short-term storage modality measured in hundreds of milliseconds. From sensory memory, information is transmitted to short-term memory (also called primary memory, immediate memory, working memory, and attention span) (Baddeley et al. 1991). Short-term memory is a limited-capacity system in which information is maintained by continued attention and rehearsal. Short-term memory lasts only 20–30 seconds, with stored information replaced by new material unless rehearsal or some other retention strategy is introduced. Transfer of new information into long-term memory begins within the first second of exposure to the stimulus, providing for a 20- to 30-second overlap between short-term and long-term memory. The consolidation of material in long-term memory takes much longer and involves a gradual strengthening of the memory trace over a period of several minutes to several hours. This trace is unstable and easily subject to loss, as illustrated by anterograde amnesia in postconcussive syndrome. Once information has entered long-term memory, it is more resistant to decay and is maintained by repetition and association.

Memory retrieval is the process of locating and accessing information from long-term storage. Retrieval is of two types: 1) direct verbatim access to memory storage traces and 2) access to a general idea or gist of the original material with final output representing a reconstruction of this idea (Russell 1981). Another important distinction related to retrieval is between recall and recognition. Free recall is measured by essay tests, for example, whereas recognition memory is evaluated by multiple-choice tests. Problems in recognition memory often relate to faulty storage. This distinction between free recall and recognition memory performance can be very useful in differentiating the cognitive impairment of depression from that of brain injury or dementing illness. Patients with Alzheimer disease typically exhibit difficulties in both free recall and recognition memory (i.e., storage and retrieval problems), whereas depressed patients and normal elders more frequently show only deficits in free recall (retrieval problems) (Kaszniak et al. 1986).

Two of the major forms of memory storage are episodic and semantic. *Episodic memory* refers to memories that have been given a temporal and spatial coding; it is associated with when and where something occurs (e.g., the birth of one's first child). *Semantic memory* is a verbally mediated memory that lacks a spatial or temporal context, such as factual knowledge.

Both episodic memory and semantic memory have been subsumed under the term *declarative memory*. *Nondeclarative memory* (sometimes called implicit or procedural memory) involves memory for overlearned skills and automatic perceptual or semantic processes that are not factually oriented (Zec 1993). Other memory distinctions include *verbal* versus *visual memory* and *retrograde* versus *anterograde amnesia*.

No single memory measure assesses all dimensions of memory, and most of the popular clinical memory tests assess declarative memory (e.g., by assessing recollection of recently presented information). Nevertheless, formal memory tests, particularly those assessing verbal memory, are better than mental status exams or language tests at discriminating persons with and without cognitive impairment (Christensen et al. 1991). Word lists have proven very useful in the identification and differential diagnosis of memory disorders, as they lend themselves to a variety of scores that can be used to characterize memory dysfunction and allow for comments to be made about where pa-

tients' main problems lie. Popular verbal list learning measures include the California Verbal Learning Test (CVLT; Delis et al. 1987) and CVLT-II (Delis et al. 2000), the Rey Auditory Verbal Learning Test (RAVLT; Lezak 1983), and the Hopkins Verbal Learning Test—Revised (HVLT-R; Benedict et al. 1998). Such instruments have the advantage of multiple learning trials versus one-time exposure to stimuli, adequate length to require secondary (long-term) memory, a delay condition, and a recognition trial. The CVLT and CVLT-II are unique in that they allow for the assessment and quantification of *how* learning occurs and what type of errors are made during learning and recall. Such a process-oriented approach to assessment may further aid in the identification of distinct memory profiles associated with different disorders (Naugle et al. 1998).

In contrast to the word list–learning tasks, the Wechsler Memory Scale, now in its fourth edition (WMS-IV; Wechsler in press), as well as its predecessors the original WMS (Wechsler 1945), WMS-R (Wechsler 1987), and WMS-III (Wechsler 1997b), includes a popular subtest, Logical Memory, which assesses memory for paragraph-length information (stories). Performance on contextual memory tasks such as Logical Memory, in contrast to list-learning tasks, provides more structure and allows for comparison of patients' ability to organize and encode stimuli of different levels of complexity.

Visual memory is often evaluated by showing examinees a standard figure or set of visual designs, having them copy the figure or designs, and then asking them to recall the information following a delay. Examples of commonly used nonverbal memory tests include the Visual Reproduction subtest of the WMS and the Rey-Osterrieth Complex Figure Test (Visser 1985) (see Chapter 13, "Traumatic Brain Injury," Figure 13–1). Some neuropsychological screening batteries, such as the Repeatable Battery for the Assessment of Neuropsychological Status (Randolph 1998), include similar tasks. Such nonverbal recall tasks have the potential confounders of psychomotor and visuospatial components, which must be factored in during test selection and interpretation and scoring. In addition, there is debate about what constitutes "nonverbal" memory. Because many of the figures used actually comprise stimuli that have or can have verbal labels attached to them, these figures are not "pure" measures of nonverbal memory per se. Also, removal of right temporal lobe structures does not always impair performance on these tasks. Differences in visual memory performances have been found as many as 10 years prior to eventual diagnosis of dementia when examining longitudinal data from control subjects who ultimately developed dementing illnesses (Kawas et al. 2003). However, older adults show greater variability on nonverbal memory tasks than their younger counterparts. Thus, although such tasks may be sensitive to abnormal memory function, specificity is sometimes lacking in healthy older adults.

Visuospatial Functioning

Visuospatial processes are complex and involve a variety of functional systems in the brain, particularly the right hemisphere in most individuals. Visuoconstructional functioning is frequently evaluated clinically through use of various standard figure copies and drawings (e.g., clock, cube, cross), with characteristic declines in quality seen as dementia progresses. Drawings by patients with Alzheimer disease often exhibit oversimplification, poor angulation, and impaired perspective (Kirk and Kertesz 1991). Furthermore, these drawings often display poor planning in their layout and presentation, which may reflect a combination of deficits in visuospatial as well as executive function skills. A combination of deficits may lead to various different errors during clock-drawing attempts, for example (see Chapter 3 of this volume, Figures 3–4 and 3–5). One of the more common neuropsychological measures of visuoconstruction is the Block Design subtest of the Wechsler scales, which requires patients to assemble three-dimensional cubes to form a pattern that matches a pattern built by the examiner or a drawing. In addition to central brain mechanisms, primary visual impairments and motor deficits may complicate graphomotor constructions in the elderly.

Language

Receptive and expressive language abilities can be disrupted by a number of neurological disorders. Receptive language involves the comprehension of oral and written communication. Comprehension deficits may involve individual words or sentences. Visual comprehension of written material is based on auditory mastery and is also often disturbed when an individual has auditory comprehension deficits. The appreciation of nonverbal components of language, such as prosody and social perception, may also be impaired as part of a dementia syndrome.

Expressive language disturbances (disorders of production) can take numerous forms as well. These include disturbances of articulation or word finding, paraphasia, and the loss of grammar, syntax, repetition, verbal fluency, and writing (see also Chapter 3). Speaking requires the ability to articulate individual vowels, consonants, and syllables and to combine them in the appropriate order. To speak a word, it is necessary to locate it among the large repository of words previously learned. A cognitively impaired person can often describe the use of an object but

cannot name it. This dysnomia may be assessed through the Boston Naming Test and its derivations (Goodglass and Kaplan 1972; Lansing et al. 1999). Paraphasias refer to the production of unintended syllables, sounds, or words, such as substituting *knife* for *night* or *mother* for *woman*. Loss of grammar and syntax can also occur and may manifest as the inability to string more than two or three words together in spontaneous sentences. Similarly, patients may be able to produce spontaneous, normal speech but unable to repeat words or sentences spoken by others.

Verbal fluency, or the ability to produce words and sentences in uninterrupted strings, is affected by numerous factors, including dysnomia associated with frontal and temporal lobe lesions. Common fluency tasks include letter or phonemic fluency—that is, the generation within a minute of as many words as possible that begin with a specified letter (e.g., words that begin with F, A, and S)—and category or semantic fluency—that is, similar generation of words that belong to a specific category (e.g., animals). Patients with Alzheimer disease commonly show deficits in verbal fluency tasks, and a number of studies have suggested that these patients have relatively greater difficulty on tests of category fluency than on tests of phonemic fluency (Epker et al. 1999).

Motor Abilities

Motor abilities range from simple functions (e.g., strength and speed) to more complex skilled movements. Basic motor deficits occur commonly in vascular and subcortical dementias and tend to be relatively less prominent in Alzheimer disease. Simple motor strength is often assessed through use of a hand dynamometer. Manual speed may be tested through procedures or instruments requiring finger tapping or fine motor dexterity. Losses in motor strength and speed beyond expectations based on a person's age and gender deserve further follow-up, particularly when lateralized.

Apraxia refers to a disruption of complex skilled movements that do not arise from basic motor difficulties. Patients may be unable to carry out a motor response to command that is easily performed spontaneously (*ideomotor apraxia*). Alternatively, they may be unable to sequence motor acts toward a specific goal (*ideational apraxia*). Although they are one of the features of more advanced dementia, apraxias are uncommon in early Alzheimer disease. Evaluation of praxis often involves having the patient pantomime a series of common activities (e.g., brushing teeth, using a comb) in response to verbal command and in imitation, and these activities are scored on sections of tests such as the Boston Diagnostic Aphasia Examination—Third Edition (Goodglass et al. 2001) and the Multilingual Aphasia Examination—Third Edition (Benton et al. 1994).

Sensory-Perceptual Abilities

Primary sensory impairments are often detected before neuropsychological testing is conducted (e.g., as observed by others or during neurological examination). Although sensory-perceptual assessment is not always performed as part of the neuropsychological evaluation of dementia, a number of standardized tests exist that may be indicated, for example, in cases of suspected cerebrovascular disease, wherein focal sensory and/or motor deficits may be present. Several standardized sensorimotor tasks include measures of basic sensory-perceptual skills (e.g., simple touch, response to double simultaneous stimulation, finger graphesthesia, gnosis, and stereognosis).

Personality and Emotional Assessment

Clinical interviewing of patients with known or suspected cognitive impairment is sometimes challenging due to their level of cognitive impairment, expressive language deficits, amnesia, lack of insight into internal mood states, apathy, and/or uncooperativeness. Standardized clinical psychological tests and specific symptom questionnaires may allow patients to respond through a written, less personal modality and may provide highly informative results.

Instruments such as the Beck Depression Inventory—II (Beck et al. 1996), the Inventory of Depressive Symptomatology (Rush et al. 1985), and the Quick Inventory of Depressive Symptomatology (Rush et al. 2003) can be used to assess depressive symptoms. Other depression measures, such as the Geriatric Depression Scale (Yesavage et al. 1983) and Cornell Scale for Depression in Dementia (Alexopoulos et al. 1988), have been developed for elders. A careful assessment of physical versus emotional symptoms of depression is important, particularly given some of the physical limitations that may accompany diseases of the elderly. Severe depression may present with cognitive symptoms that should be carefully and systematically evaluated and quantified. The neuropsychological evaluation may be particularly helpful in distinguishing qualitative features of depression from dementia.

Assessment of Everyday Functional Abilities

Although the assessment of everyday functional abilities is often beyond the scope of the traditional neuropsycholog-

ical examination, a variety of standardized measures of instrumental activities of daily living are available for assessment of patients with dementia. Several popular examples include the Instrumental Activities of Daily Living Scale (Lawton and Brody 1969), Independent Living Scales (Loeb 1996), and Daily Activities Questionnaire (Oakley et al. 1993). Such instruments typically rely on caregiver report or require patients to perform tasks that are analogous to various daily functions (e.g., making change, check writing, dialing a telephone). Many of these measures are time-consuming or rely exclusively on caregiver ratings. However, the Texas Functional Living Scale (TFLS), previously known as the Test of Everyday Functional Abilities (Cullum et al. 2001), is a brief, quantitative, performance-based measure of simple everyday skills relevant to the functioning of patients with dementia. It has shown sensitivity to dementia and a strong correlation with the MMSE in patients with Alzheimer disease (r=0.88; Weiner et al. 2006), has detected improvement similar to that of the MMSE in response to acetylcholinesterase inhibitor treatment (Saine et al. 2002), and differentiates dementia patients needing varied levels of nursing care (Weiner et al. 2007). Use of such measures can also facilitate a more direct communication of neuropsychological concepts to caregivers in terms of everyday function.

Neuropsychological Screening Batteries for Dementia

Although the measures presented above are commonly used in the comprehensive neuropsychological evaluation of persons with known or suspected dementia, a number of briefer test batteries have been developed that have enjoyed widespread use in clinical and research settings.

CERAD Neuropsychological Battery

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), a federally funded research effort supported by 24 sites in the United States, adopted a basic neuropsychological battery that evaluates memory, language functions, and constructional praxis. The CERAD battery evaluates acquisition of new information (a word list–learning task), memory (delayed recall and recognition of the word list), language functions (category fluency and a shortened version of the Boston Naming Test), and constructional praxis (copying simple geometric figures). The battery typically requires 30–45 minutes to complete and has good norms (Chandler et al. 2005; Welsh et al. 1994). In conjunction with appropriate medical and laboratory examinations, the CERAD battery showed an autopsy-confirmed diagnostic hit rate for Alzheimer disease of 80%–90% (Morris et al. 1989). In addition to the subtest scores, Chandler et al. (2005) developed a total score for the CERAD battery (maximum score=100) that extends the battery's utility and provides demographically corrected norms for the total score. The CERAD total score was found to be highly effective in differentiating persons with Alzheimer disease from normal controls with a cut score of 77 (sensitivity and specificity >92%) and to be useful in distinguishing subjects with mild cognitive impairment from nondemented controls with a cut score of 85 (sensitivity=81; specificity=73).

Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph 1998) is a 30- to 45-minute screening battery with norms for ages 20–89 years. It has 12 subtests that assess five cognitive domains: Immediate Memory (List Learning + Story), Visuospatial/Constructional (Figure Copy + Line Orientation), Language (Picture Naming + Category Fluency), Attention (digit span + Symbol/Number Coding), and Delayed Memory (Recall of Word List, Story, and Figure, + Recognition of Word List). A total score can be calculated from the subtests (total index scores range from 40 to 160), and an alternate version of the battery is available.

Telecognitive Assessment

The availability of traditional face-to-face neuropsychological evaluations may be limited in certain circumstances, such as in rural communities, and there has been a growing body of literature supporting the use of videoconferencing in psychiatry (e.g., Hilty et al. 2002). Although some common tests have shown initial promise for telephone administration in some settings (Unverzagt et al. 2007), only a handful of studies have explored the feasibility of videoconferencing-based neuropsychological testing, or telecognitive assessment, for patients with dementia. Cullum et al. (2006) examined the validity of telecognitive assessment by comparing face-to-face evaluations with those conducted by videoconferencing using

a brief battery of standard clinical measures in a sample of 19 subjects with Alzheimer disease and 14 patients with mild cognitive impairment. There were high correlations and little bias between testing conditions, suggesting feasibility, validity, and reliability of this emerging testing approach.

Interpretation of Neuropsychological Results

The past and present context of individuals' lives influences their development as persons and affects their cognitive characteristics and presentation. Although the objective score on a particular test may be the same for two individuals, its meaning may be different based on background factors such as education, jobs and professional achievement, and cultural experiences. Neuropsychological assessment therefore begins with a systematic inquiry into a person's medical and developmental history; language acquisition; performance in school, including learning problems; military record (if applicable); occupational history; and acquired insults to the central nervous system. Present medical history is also important insofar as a variety of medical conditions can influence neuropsychological function. Past psychiatric history and treatment are also important to assess within the context of the onset and progression of current symptoms and presenting complaints. Current medications should be reviewed, because functions such as attention and memory are particularly susceptible in older adults to disruption by anxiolytics or antidepressants with anticholinergic side effects (Weiner and Davis 1986). Having a good overview of an individual's background history also allows for the most accurate interpretation of neuropsychological test results based on available test norms.

Examination of an individual's performance on a test in comparison with that of others in the general population who share demographic similarities provides important comparative reference data that aid interpretation. Scores falling outside the normal range must be examined carefully, as labels of different levels of impairment are assigned on this basis. This is particularly important for older individuals, in whom declines on formal testing typically begin in the sixth and seventh decades of life. Cross-cultural norms should also be considered, if available, because cultural and linguistic backgrounds may have a large effect on some tests. Various sources of norms exist in published articles, textbooks, and test manuals, depending on the test. Some neuropsychologists emphasize that the selection of appropriate test norms is as important as the selection of tests to administer. Current omnibus norm sources include the normative text by Mitrushina et al. (2005) and test compendia by Lezak et al. (2004) and Strauss et al. (2006).

Regardless of the norms used, standard scores (*T* scores, *z* scores, percentiles, scaled scores, etc.) that are commonly derived from raw test scores should be used only as interpretive guidelines. These scores are derived from (ideally) large groups of people free from neuropsychiatric disorders, and application to the individual case may require adjustment. Other factors that come into play when interpreting standard or raw test scores include obtaining adequate examinee effort and ensuring that the examinee's hearing and understanding of test instructions were adequate.

Neuropsychological Profiles in Dementia

Alzheimer Disease

Alzheimer disease accounts for 50%–80% of all dementias (Evans et al. 1989). The often subtle nature of its onset, characteristically slow progression, and heterogeneity in behavioral expression may complicate its early detection. Early detection and correct diagnosis are important, because there are treatable causes of dementia that must be ruled out before a diagnosis of Alzheimer disease is made. As additional pharmacologic treatments become available, early detection and intervention will become even more crucial. Early-stage Alzheimer disease is typically characterized by progressive impairment of new learning and recent (episodic) memory (see Table 5–12). Delayed recall of verbal material (whether assessed via paragraph or word list recall) has consistently been shown to be particularly sensitive to such deficits.

In general, individuals with Alzheimer disease show reduced encoding, consolidation, and storage of new information, as well as rapid forgetting of newly learned material. Careful quantitative and qualitative analyses of verbal learning and memory performances often detect a "prototypical" pattern of findings on measures such as the CVLT and CVLT-II. As indicated in Table 5–13, patients with Alzheimer disease tend to show limited learning, sometimes recalling only the last few items presented, and they make characteristic intrusion errors during learning and recall of words, wherein they often respond with semantically related words rather than target list items. Cuing is less often helpful to patients with Alzheimer disease and may stimulate additional intrusions. Delayed recognition test-

ing is also impaired, with high numbers of false-positive errors, reflecting their deficits in encoding as well as retrieval. Patterns derived from such results can be used to aid in differential diagnosis, as various dementia syndromes may demonstrate different profiles (see Table 5–13).

Following the onset of progressive deterioration of episodic memory, additional cognitive declines occur in executive functioning and aspects of language, most notably prominent word-finding difficulties and reduced verbal fluency. Visuospatial impairments are also common, as evidenced by visuoconstructional deficits and loss of direction sense. Gross visuospatial deficits may be identified by asking the individual to perform simple cognitive tasks such as clock drawing (Freedman et al. 1994), in which evidence of executive dysfunction (e.g., problems setting the hands of the clock to a specified time, stimulus-bound responses) may also be observed. Greater neuropsychological dysfunction is associated with deficits in instrumental activities of daily living (e.g., preparing meals, balancing a checkbook, repairing things around the house, planning social events) that clearly affect patients' quality of life. Apraxias eventually develop as the disease progresses, and patients become unable to perform once-familiar self-care tasks such as dressing and grooming.

Vascular Dementia

Vascular dementia accounts for 0%–20% of dementia cases (Nyenhuis and Gorelick 1998). It is often characterized by a sudden onset and history of stroke or transient ischemic attacks, although symptoms may emerge over time as cardiovascular disease progresses and white matter lesions appear. Vascular dementia tends to have more of a stepwise rather than slow progression, with a worsening of symptoms associated with new vascular events. There may be cortical and subcortical manifestations, including focal neurological signs. Considerable overlap can occur between the cognitive impairments of Alzheimer disease and vascular dementia, and they may coexist. Even if a patient has cognitive symptoms from both, neuropsychological evaluation may assist in the diagnosis of vascular dementia through identifying focal neurocognitive impairments, "spotty" neuropsychological profiles (e.g., a mixture of cortical and subcortical signs), and test results reflecting asymmetries in sensory and/or motor performance (e.g., see Table 5–13). Furthermore, vascular profiles may lack some of the features of the amnestic syndrome of Alzheimer disease, as discussed earlier in this chapter. Serial neuropsychological testing can also help to characterize the pattern and severity of decline over time in patients with cognitive impairments of both Alzheimer disease and vascular dementia.

TABLE 5–12. Characteristics of memory dysfunction in Alzheimer disease

- Impaired encoding (limited learning, decreased organization)
- Rapid forgetting
- Recency recall (recalling information from the end of a list or paragraph)
- Intrusion errors during recall
- Impaired recognition

Frontotemporal Dementias

Dementias include a variety of disorders, such as frontotemporal dementia (behavioral subtype), Pick disease (with or without Pick bodies), corticobasal ganglionic degeneration, nonspecific frontal gliosis, and various tauopathies, in addition to language-variant frontotemporal dementias that include primary progressive aphasia and semantic dementia. Characteristic symptoms include deficits in abstraction, executive function, self-awareness, and social behavior. Behavioral disturbance, personality change, and disinhibition are often among the early signs. Neuropsychological evaluation of these patients typically reveals prominent deficits in executive function and cognitive flexibility, in addition to behavioral symptoms that typify frontal lobe syndromes. In language-variant frontotemporal disorders, expressive language deficits in the form of fluent or nonfluent aphasia with marked word-finding difficulty or loss of semantic knowledge are typically the first symptoms reported, although executive function impairments may also be present early in the course of the disease. Importantly, the deficits in executive functioning and language are typically more prominent than deficits in memory in this class of disorders, which may assist in differential diagnosis (Neary et al. 1998) (see Table 5–13).

Subcortical Dementias

Subcortical dementias, which primarily involve subcortical structures or systems and have associated cognitive impairments, include Huntington disease, Parkinson disease, progressive supranuclear palsy, multiple sclerosis, and Binswanger disease. Some neuropsychological findings overlap with those seen in the primary cortical dementias, although several characteristics tend to help differentiate these groups.

Subcortical dementias frequently involve slowing in general information processing, reduced attention, and problems with executive and visuospatial functions (Hu-

TABLE 5–13. Verbal learning and memory features in dementia syndromes

Dementia syndrome	Impaired encoding	Deficient recall	Intrusion errors	Perseveration errors	Impaired recognition
Alzheimer	++	++	++	−	++
Vascular	++	+	−	+/−	−
Frontotemporal	+	+	−	+	+/−
Subcortical	+/−	−	−	−	−
Depression	+/−	+/−	−	−	−

Note. Presence (+) or absence (−) of qualitative memory features on standardized word-list learning tasks. ++ = particularly characteristic; +/− = sometimes present.

ber and Shuttleworth 1990). Marked language deficits are characteristically absent, and the pattern of deficits, because of subcortical-cortical disconnections, can mimic frontal lobe dysfunction as reflected by deficits in problem solving (Brandt and Bylsma 1993). The memory impairment associated with subcortical dysfunction (at least in milder cases) tends to affect retrieval and memory search mechanisms, because delayed recall testing often reveals some degree of impairment; however, performance on cued recall and particularly recognition testing tends to be much better, suggesting that patients are able to encode and store more information than they can spontaneously recall. Cued recall and recognition testing of episodic memory is therefore critical in differential diagnosis. In cases of severe cognitive impairment, patients with subcortical dementias may be neuropsychologically indistinguishable from those with cortical dementia due to the magnitude of their deficits (see Table 5–13).

Depression

The terms *dementia syndrome of depression* (Folstein and McHugh 1978) or *pseudodementia* have been used to designate reversible cognitive deficits experienced by some patients suffering from severe depression (Wells 1979). The fact that dementia patients may experience depressive symptoms can complicate attempts to distinguish the functional dementia of depression from structural brain diseases (Gilley 1993). Individuals with depression sometimes resemble patients with subcortical dysfunction in their slowed information processing and failure to spontaneously employ active learning and memory search strategies (King and Caine 1990). When cognitive deficits are indicated by formal neuropsychological testing of these patients, several characteristic features or trends have been observed (Table 5–13). Attention may be reduced and/or variable across tasks. Depressed patients often show intact memory storage even though retrieval problems may occur, in contrast to individuals with Alzheimer disease, who have both impaired storage and retrieval (Lachner et al. 1994; Lamberty and Bieliauskas 1993). Moreover, rapid onset of cognitive symptoms and the presence of patient complaints beyond those expressed by family members are also more common in depressed patients. However, the persistence of deficits following recovery from depression may signal a dementing illness, so serial evaluations may be useful. Neuropsychological patterns of performance can often be used to differentiate cognitive difficulties secondary to depression from those due to Alzheimer disease. In many patients with depression, despite cognitive complaints, performance on effortful tests of formal neuropsychological examinations may be normal or only slightly abnormal (La Rue 1992). In cases where some cognitive inefficiencies are apparent, the disorders may coexist, and differential diagnosis may be challenging in a small proportion of patients who are severely depressed. Accordingly, serial neuropsychological evaluations may be useful to monitor cognitive and memory abilities over time, as the memory problems in patients with uncomplicated depression would not be expected to progress.

Purposes of Neuropsychological Evaluation

The value of the neuropsychological examination is manyfold in cases of known or particularly suspected dementia, and results can be used for multiple purposes. Neuropsychological assessment may be particularly useful when there is a discrepancy between the patient's self-report of difficulties and the family's assessment, when there is need for additional confirming evidence of a tentative diagnosis

before recommending additional neurodiagnostic procedures, when bedside mental status examination or cognitive screening is normal but suspect, and when emotional factors such as depression or anxiety may contribute to symptoms. Several examples illustrate these points. Family members often become concerned about an elderly relative's behavior; however, in a short office visit, the patient may deny or minimize difficulties. A neuropsychological evaluation often provides valuable diagnostic information as well as useful practical recommendations regarding the person's degree of independence. Another patient's physician may suspect that the patient is declining cognitively but also appears to be withdrawn and may be depressed. The neuropsychological evaluation can help to identify the various factors contributing to the apparent decline and quantify them for future reference. A short neuropsychological screening examination can also be useful in the busy office or inpatient setting as a quick and inexpensive way to help identify patients who warrant further evaluation for dementia or emotional disorders.

The neuropsychological evaluation can also help to assess the cognitive effects of various medical treatments. Pre- and posttreatment evaluations can be employed to assess the effects of treatments such as electroconvulsive therapy, shunts for normal pressure hydrocephalus, antidepressant or antianxiety medications, and endarterectomy surgery. Results may yield valuable objective data on a patient's cognitive response to treatment, allowing the physician to make decisions on whether to continue, change, or drop a particular form of therapy.

Finally, a detailed analysis of a patient's cognitive abilities may be used to plan comprehensive interventions that focus on the patient's strengths. This can be done in conjunction with medical therapy and includes attempts to minimize the effects of cognitive deficits from dementing disorders. Intervention often involves continuing education and support of the family to maximize the use of the available support network to help maintain safe, independent functioning for as long as possible. This can be particularly useful in progressive dementia cases, in which little direct medical intervention is possible and the most useful intervention is planning and structuring an individual's environment.

Conclusion

Neuropsychological evaluation of patients with known or suspected dementia serves many purposes and is a standard part of the comprehensive neurodiagnostic evaluation of cognitive concerns in clinical and research settings. Thoughtful interpretation of results from carefully selected tests yields valuable information regarding the presence or absence of abnormal cognitive decline, can assist with differential diagnosis, and can be used for the quantitative tracking of cognitive changes over time. Neurocognitive assessment is also useful for identifying specific cognitive functions that may be maintained or enhanced by new medications and for quantifying treatment response. Obtaining an assessment of an individual's cognitive strengths and weaknesses can also assist in treatment planning and providing sound recommendations to patients and their families.

KEY POINTS

- Neuropsychological testing is an accepted neurodiagnostic procedure with its own current procedural terminology codes.
- Neuropsychological testing is the most sensitive means of evaluating human cognition.
- Although numerous brief bedside tests of memory and cognition are available, their results may be unreliable, especially in individuals with mild cognitive impairment.
- Normal scores on brief cognitive screening tasks may be obtained by patients with mild dementia.
- Normal aging is associated with changes in some, but not all, cognitive abilities.
- Utilization of test norms is important in interpreting neuropsychological test results.
- Patterns of neuropsychological test results may assist in differential diagnosis.

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CHAPTER 6

Neuroimaging

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Imaging has had a profound impact on medical practice, and it plays an expanding role in the diagnosis and management of cognitive disorders. Despite accumulated knowledge and the development of detailed clinical criteria, diagnosing the cause of dementia remains difficult using current clinical methods alone. Different dementing diseases have similar symptoms and examination findings, and some of the diagnostic criteria overlap. Also, identifying the most salient features of an illness is difficult in complicated cases or when history is limited or unreliable. Neuroimaging has become an essential tool because it reveals without bias the pathological alterations of brain composition and structure. With minimal patient risk and discomfort, changes in the otherwise inaccessible brain can be visualized in detail. Even in rare situations when a brain biopsy is needed, neuroimaging provides essential information about the distribution and regional severity of pathological damage.

Neuroimaging can be challenging to use optimally. It is not a panacea for making diagnostic decisions and can answer only some of the many difficult questions that arise during dementia care. Nevertheless, judicious use of imaging sometimes provides definitive information, sparing patients and their families the expense and frustration of unnecessary diagnostic odysseys.

In this chapter, I provide a rational approach for selecting brain imaging methods from the wide array of possibilities and incorporating them into dementia evaluations. I critically review how current knowledge can be used to make everyday diagnostic and treatment decisions, and I preview emerging technologies. Although this chapter is not a primer for the technical aspects of imaging, adequate discussion is provided so the reader can be a knowledgeable user of this technology.

Rational Use of Neuroimaging in Dementia Care

Evaluating a patient with cognitive impairment is time consuming, complex, and intellectually demanding. Diagnosis involves the formulation and resolution of a series of questions to determine the cause of symptoms and establish an appropriate plan for care. Questions arise incrementally and are modified as information accumulates from the available patient history and during a careful examination. Some of these questions can be answered by

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obtaining additional historical information or performing a more detailed and extensive examination; others are best approached with the aid of laboratory tests and imaging. In every case, results must be interpreted accurately and testing used appropriately. Ideal utilization of neuroimaging follows these same rules in the attempt to answer questions that cannot otherwise be resolved. Neuroimaging does not simplify dementia evaluations but rather adds information that otherwise would be unavailable. Although it can clarify clinical problems, neuroimaging adds to the complexity of diagnostic judgments and must be incorporated with other data into decision making.

Asking the Right Questions of Imaging

The evaluation of suspected dementing illness has two distinct and essential steps. The first is to recognize suspicious complaints and symptoms and to decide whether they indicate significant cognitive impairment. Brain imaging contributes little to this decision and cannot substitute for a careful clinical history and examination. Only a mental status examination provides the evidence necessary to determine whether cognitive deficits are sufficient to explain newly acquired impairment in everyday activities. Imaging abnormalities cannot be used to accurately infer the presence of cognitive disturbance. Individuals with dramatically abnormal scans may have normal cognition. Likewise, a normal imaging study does not rule out cognitive impairment.

If clinical evidence indicates significant cognitive impairment, the second essential step in evaluation is determining the cause. Once again, the patient's history, mental status, and physical examination are essential, but neuroimaging also plays a crucial role at this point. Imaging provides important evidence of a dementing disease and may identify its cause by permitting the visual recognition of characteristic alterations in brain structure, chemistry, and function. Diagnosis cannot be based on brain imaging alone, but detecting specific abnormalities or documenting a lack of abnormality can be useful in supporting or refuting a particular diagnosis.

The wide range of potential causes of dementia requires that diagnostic questions be considered systematically. Diagnostic questions that imaging can significantly aid are listed in Table 6–1. Several disorders often contribute to an individual patient's dementia; consequently, the clinician must address each diagnostic question in turn, even when investigations have identified a potential culprit. Depending on the clinical history and examination, all questions are not equally important, and that fact should be reflected in the types of imaging ordered and their priority. Fortunately, a single neuroimaging study usually addresses several clinical questions simultaneously. However, when the information provided by a single scanning modality is insufficient, additional imaging may be necessary. Neuroimaging is particularly valuable in difficult and atypical cases. Brain scanning may be the only way to conclusively disentangle multiple dementing disorders simultaneously contributing to a patient's intellectual decline.

Choosing the Best Imaging Modality

Clinical neuroimaging can be divided broadly into structural and molecular methods. Structural methods produce images from absorption of X rays using computed tomography (CT) or from measuring magnetic susceptibility of protons with magnetic resonance imaging (MRI). Molecular methods count emissions from radioactive isotopes that produce either positrons in positron emission tomography (PET) or gamma emission in single photon emission computed tomography (SPECT). Structural and molecular methods provide different and complementary information about the brain. Although some MRI methods partially reflect brain function, these methods are either not generally available for clinical use or have uncertain clinical utility in dementia. Molecular imaging provides some information about brain structure, but this information can only be inferred after disentangling biochemical data and the result is much less detailed information about brain anatomy than CT or MRI provides. Consequently, structural and molecular imaging are best at addressing different clinical questions, and neither can replace the contributions of the other.

Framing the patient's problems as specific clinical questions can determine the imaging study most likely to be helpful (see Table 6–1). The American Academy of Neurology recommends that the initial evaluation of patients with dementia should include structural neuroimaging with either noncontrast CT or MRI (Knopman et al. 2001). Focal neurological findings should raise suspicion of a structural lesion, but CT and MRI are justified by a reasonably high prevalence of abnormalities even when they are unsuspected after a careful medical history and examination (Chui and Zhang 1997). The role of molecular imaging in dementia evaluations is not as firmly established. The biochemical changes revealed by PET and SPECT can often be inferred from the clinical history and examination or from the patient's response to medication. Nevertheless, when diagnostic uncertainty remains, molecular imaging can be useful in specific circumstances, as discussed in the section "Molecular Neuroimaging" later in this chapter.

TABLE 6–1. Diagnostic questions in dementia most relevant to structural or molecular neuroimaging

Structural imaging
Is there ventricular enlargement?
Is there a mass lesion?
Is there cerebrovascular disease?
Is there generalized volume loss?
Is there focal volume loss?
Molecular imaging
What is the pattern of cerebral hypometabolism?
Is there loss of dopaminergic neurons?
Are there amyloid plaques?

Determining the Relevance of Imaging Findings

Achieving the full benefits of imaging requires integration of study results and their clinical context. Physicians ordering imaging studies are responsible for conveying to the radiologist or nuclear medicine specialist the diagnostic questions that need to be answered and indicating the clinical context. Even with this information, however, a radiologist alone cannot determine fully how findings relate to a patient's symptoms. A detailed understanding of the individual and his or her symptoms are needed to judge whether image abnormalities are clinically relevant. Incidental abnormalities are common. For example, a population-based MRI study of 2,000 middle-age and elderly subjects found asymptomatic brain infarcts in 7.2%, cerebral aneurysms in 1.8%, and benign primary tumors in 1.6% of the subjects (Vernooij et al. 2007). Consequently, clinical correlates must be considered before deciding to act on any imaging abnormality.

A clinician often benefits from personally reviewing a scan to get a better sense of the extent and location of any abnormality. The size and number of lesions should correspond roughly with the severity of patient symptoms, and the type of findings should be consistent with the location of brain damage. Radiologists may be able to estimate the age of individual lesions and thus aid the comparison of imaging findings with a patient's clinical course. Whether or not the localization and timing of clinical symptoms and the imaging findings coincide is a reliable guide for deciding whether scan abnormalities are clinically important. Ideally, the care provider, radiologist, and nuclear medicine specialist work together to ensure that the best imaging techniques are used and that clinically meaningful information is appropriately incorporated into patient care.

Concerns About the Use of Neuroimaging in Dementia Evaluation

Many concerns have been expressed about the appropriate use of neuroimaging in patients with suspected dementing illness (see Table 6–2). Although these same concerns are relevant to the use of any diagnostic test, they seem to arise more often and are expressed more vigorously with evaluations of dementia than with those of other disorders.

Economic concerns have been particularly prominent in discussions about brain imaging in dementia. The high prevalence of cognitive problems, the aging population, and the relatively high expense of imaging studies all mean that costs of dementia evaluations are especially significant for insurers and society. Understandably, this expense causes diagnostic testing for dementia to be subjected to a higher degree of scrutiny. Furthermore, because current treatments for dementing disorders generally have only modest benefits, a robust link between imaging and treatment outcomes is difficult to document. On the other hand, the economic costs of failure to treat dementia and the expense of inappropriate care are also very high. Because an accurate diagnosis is the basis for rational management, imaging costs are easily justified if used appropriately and if imaging improves diagnostic accuracy. Evaluation costs are small when compared to the long-term costs of caring for dementia over years. Unfortunately, cost-benefit analysis studies sometimes fail to consider the costs of inappropriate treatments, and the usual methods of cost containment tend to erect arbitrary barriers to access and can exacerbate some utilization errors and discourage definitive diagnosis. Insurance more readily reimburses test performance than the effort that would be needed to properly evaluate patients. As a result, physicians may order imaging repeatedly without reaching a specific diagnosis and may fail to use all the information relevant to dementia care that imaging provides. Improving providers' knowledge would be a more effective way to improve the cost-effectiveness of imaging in the long run. Overuse of and overdependence on imaging are most common when dementia evaluations are incomplete or inadequate and when physicians lack confidence in their clinical skills. Lack of knowledge also causes errors of omission, which are exacerbated by barriers to obtaining timely testing.

Despite the potential value of unique information that neuroimaging can provide, many practitioners have considerable ambivalence about the use of neuroimaging in patients with suspected dementing illness. This ambivalence, which is uncommon with other brain disorders, de-

TABLE 6–2. Potential errors and misuses of imaging

Utilization errors
Overuse—needlessly repeating studies or obtaining imaging studies using methods unlikely to contribute to a diagnosis, thus causing excessive costs without additional clinical benefit
Underuse—failure to utilize the imaging modality that could provide critical information for diagnosis
Omission—failure to incorporate significant imaging findings in diagnosis
Overdependence—using imaging results to decide whether there is dementia when clinical assessment alone is reliable, or using imaging results to make a diagnosis without utilizing other relevant clinical data
Interpretation errors
Overinterpretation—assigning a cause of dementia based on clinically insignificant imaging findings
Misinterpretation—failing to recognize the presence of clinically significant lesions, causing errors in radiographic diagnosis
Inconsistent interpretation—variability between radiologists or from patient to patient in the description or clinical significance ascribed to identical imaging findings
Technical errors
Lack of reliability—inconsistent acquisition or processing of imaging data, causing misinterpretation
Artifact—failure to prevent or identify image acquisition or analysis errors that prevent the accurate interpretation of scans

serves explanation because it contributes to misuse. In part, the ambivalence reflects a pervasive diagnostic and therapeutic nihilism that has not been fully overcome by the growing understanding of dementing diseases. Diagnostic efforts sometimes have been justified based solely on the potential of identifying reversible causes of dementia. With this approach, imaging often becomes a frustrating exercise because dementia is potentially reversible in only a small proportion of patients. It is now clear that accurate diagnosis is important regardless of whether symptoms can be reversed. Symptomatic and disease-specific treatments are available for most dementing diseases, and early diagnosis permits appropriate treatment to be initiated and can prevent complications. To achieve the goal of specific diagnosis, a "rule in" rather than "rule out" approach to neuroimaging is appropriate to identify characteristic findings of neurodegenerative disease and not simply mass lesions (Scheltens et al. 2002).

Interpretation errors also are critical. Although mass lesions can be identified and described, common and equally relevant neurodegenerative findings are not so clear-cut. Clinicians may find reports of imaging studies more confusing than helpful. For example, white matter changes are prevalent in dementing disorders, but factors critical to determining their clinical relevance (such as their location and extent) often are not included in radiologists' reports. Atrophy may be misjudged or focal atrophy overlooked.

Technical issues are especially relevant to imaging because of the complexity of performing studies. Attention to technical details is critical to assure that neuroimaging results are reliable and is the primary responsibility of radiologists and nuclear medicine specialists. However, clinicians also can benefit from recognizing artifacts and being aware of methodological limitations. Until recently, imaging of patients with memory loss and dementia varied considerably from one institution to another. This is now changing due to the Alzheimer's Disease Neuroimaging Initiative (Mueller et al. 2005), a multisite, longitudinal study of normal cognitive aging, mild cognitive impairment, and early Alzheimer disease (AD). This initiative has resulted in standardized image acquisition protocols for MRI and PET using a variety of scanner models and manufacturers, as well as the implementation of quality control methods with phantom studies and image processing methods that correct for geometric and signal variability. Data from the Alzheimer's Disease Neuroimaging Initiative are a public domain resource available to qualified investigators (https://www.loni.ucla.edu/ida/login.jsp). The Web site also provides technical details to encourage adoption of uniform imaging standards for dementia.

Structural Neuroimaging

Dementing illnesses frequently alter brain structure. CT and MRI simplify diagnosis of tumors, stroke, and other focal destructive and mass lesions and are superior to radionuclide cisternography in identifying hydrocephalus. As a result, structural imaging was quickly adopted but not used routinely in dementia evaluations. Use of CT and MRI to recognize neurodegenerative diseases has been more challenging but has evolved sufficiently to show utility for this purpose also.

Choosing Between CT and MRI

CT and MRI provide similar but not identical information about brain structure (Figure 6–1). CT provides superlative anatomical information about bone and intracranial calcifications, ventricles, and sulci. Because X rays are linear, CT scans more accurately represent the location of brain lesions and are preferable in cases of head trauma and for surgical applications. In contrast, determining the size and relative position of brain structures with MRI depends on precise measurement of magnetic gradients and incorporating corrections to compensate for gradient variations that differ from scan to scan. Failure to apply these corrections accurately causes misleading spatial distortions. For most applications relevant to dementia, the advantages of CT usually are outweighed by its limitations. CT is subject to beam hardening artifacts that appear adjacent to densely radiopaque objects, such as the temporal bone. This produces dense linear intensities, disrupting structural detail in the inferior temporal lobe and posterior fossa.

MRI has many advantages in dementia evaluations. It offers greater resolution and contrast, making it possible to precisely delineate gray matter and identify white matter hyperintensities in the aging brain. MRI possesses superior three-dimensional imaging capabilities, allowing high-resolution coronal and sagittal views of the brain to be obtained routinely and providing better visualization of small brain areas that are important in cognition (e.g., hippocampi and mammillary bodies). Altering acquisition parameters also allows MRI to emphasize specific properties of magnetic susceptibility and to provide more definitive and detailed information than is possible with CT. Furthermore, MRI can be performed repeatedly without the risks of radiation exposure associated with CT. Physicians have been largely unaware of the high cumulative levels of radiation to which many patients have been exposed from clinical studies, and this exposure is raising increasing concern (Brenner and Hall 2007). For these reasons, MRI is preferable to CT for dementia evaluations, unless there is a contraindication. Most of the subsequent discussion of structural imaging therefore focuses on MRI, although often CT can provide similar results.

Technical Considerations

MRI produces images that maximize sensitivity to specific tissue characteristics by varying the timing and repetition of radiofrequency pulse sequences and signal acquisition parameters (Figure 6–1). T_1-weighted images are most useful for defining anatomical structures. T_2-weighted and spin-echo images are best suited for detecting white matter lesions. Some protocols are especially valuable in dementia evaluations. Fluid-attenuated inversion recovery (FLAIR) images highlight white matter abnormalities seen in T_2-weighted images while suppressing signals in cerebrospinal fluid (CSF); this enhances visual contrast and helps distinguish widened capillary spaces from white matter pathology. Diffusion-weighted imaging is sensitive to subtle changes in brain water content and diffusivity and is used for diffusion tensor imaging and tractography. The degree of water content and diffusivity evolves after ischemic injury, so diffusion-weighted imaging can be used to estimate the age of vascular lesions. Diffusion-weighted imaging also is the most sensitive method for detecting spongiform pathology. Pulse sequences designed to highlight paramagnetic properties of hemoglobin are the basis for functional MRI and can identify microhemorrhages associated with amyloid angiopathy and normal aging. Gradient echo imaging is the most widely used protocol for identifying hemorrhage. There is less experience with susceptibility-weighted imaging, but it appears to be even more sensitive (Haacke et al. 2007).

Ferromagnetic objects are a major obstacle and risk to the performance of MRI. Because high magnetic fields can propel objects containing iron into the scanner, imaging centers take extensive precautions to exclude inadvertent entry of metal objects. This can become a significant barrier, especially for acutely ill patients. For patients with dementia, the most common contraindication is the presence of ferromagnetic implants or foreign bodies. Sometimes, unexpected small metal particles from trauma in the distant past are discovered and cause only minor interference with imaging. In other cases, when history is difficult to obtain, X-ray films must be obtained to scout for metal before proceeding with MRI. Although procedures have been developed so that patients with artificial joints generally can be scanned safely, MRI is hazardous with pacemakers, some mechanical valves, and metal-containing sutures and surgical devices. Tattoos with metal-containing dyes can cause skin burns in high-field (>1.5T) scanners. Furthermore, dental work and foreign objects, including jewelry, can cause severe image distortions, and artifacts and should be removed when possible. Another problem, especially for individuals with claustrophobia, is the confining space during MRI. Imaging is most effective when the gap between patient and magnet is minimized, so small bore scanners are preferred. Some less confining "open" scanners, if available, can be appropriate in certain situations. MRI scanning requires more time than does CT; therefore, MRI may require sedation of certain patients, or CT may be preferred for patients who have claustrophobia or a movement disorder or for those who are less able to cooperate.

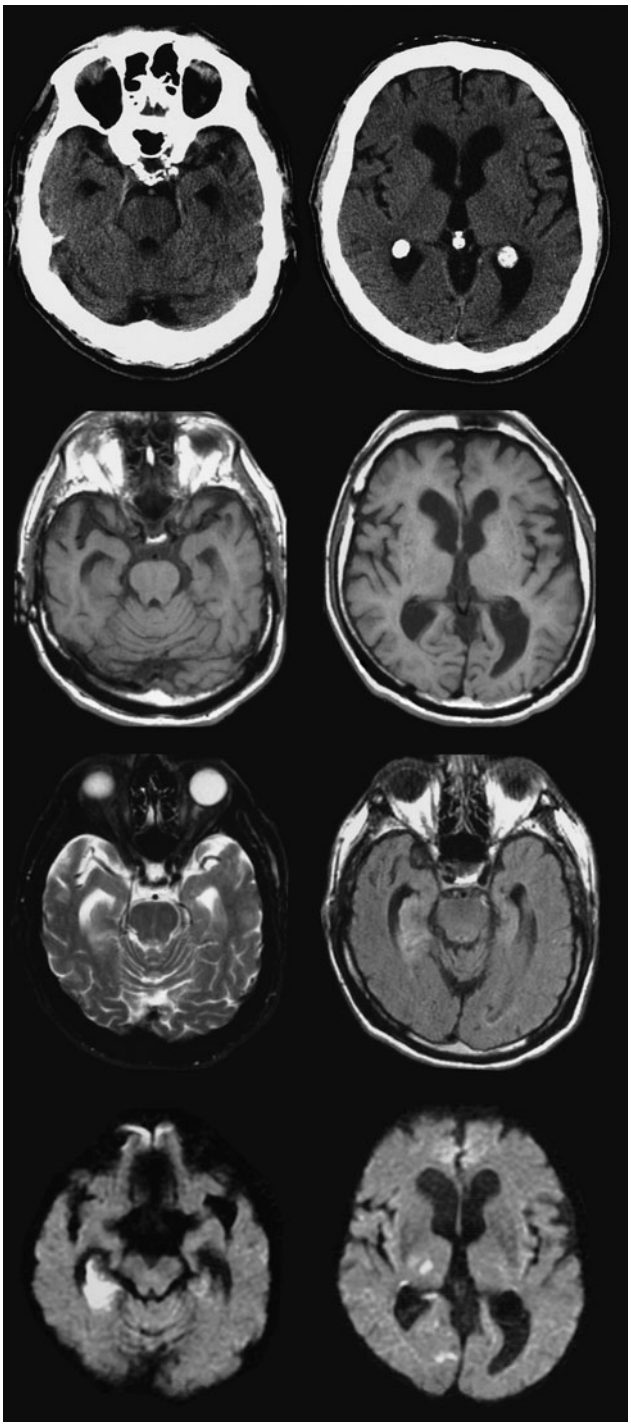

FIGURE 6–1. Computed tomography (CT) and magnetic resonance imaging (MRI) sequences identifying vascular lesions and volume loss.
Transaxial CT (top row) and MRI scans (rows 2–4) in an 82-year-old man referred for evaluation of profound memory loss. Although the family reported that the memory problems had begun abruptly over the previous few days, his physicians were doubtful. The CT scan shows widening of sulci and symmetrical enlargement of lateral ventricles. The skull and calcifications in the choroid plexus and pineal gland are bright and easily seen. No vascular or mass lesions are evident. On MRI, bone and calcified structures are not so readily visualized. Instead, fat in the scalp causes the high signal ring outside the brain seen in some images. T_1-weighted images (row 2) show sulci in greater detail than do CT scans, and gray and white matter can be distinguished. Ventricular size is similar, but brain boundaries are more sharply defined than with CT. A T_2-weighted image (row 3, left) provides less structural detail but highlights free water that causes high signal intensity in the orbits and cerebrospinal fluid (CSF). Slight increased signal in the right hippocampus in the T_2 scan is even more apparent in the fluid-attenuated inversion recovery (FLAIR) image (row 3, right), which suppresses signal in the CSF. This lesion becomes obvious on diffusion-weighted images (row 4). On this sequence, recent strokes caused increased signal, and an acute stroke involving the right hippocampus and a small, punctate area in the right thalamus confirmed the family's report of recent, sudden memory loss.

Diagnostic Questions Most Relevant to Structural Neuroimaging

Is There a Mass Lesion?

The most obvious use of structural brain imaging is to identify a mass lesion. Focal neurological deficits indicative of brain injury, such as hemiparesis, visual field cut, or aphasia, warrant investigation with CT or MRI. Brain tumors, subdural hematomas, and brain abscesses are easily recognized. Most mass lesions in patients with dementia are identified when a brain scan is obtained to evaluate a focal neurological complaint rather than during a routine dementia evaluation. The most conspicuous exception is in elderly individuals for whom evaluations are delayed or incomplete. Imaging centers occasionally find unsuspected brain tumors and subdural hematomas when physicians inappropriately assumed that an elderly patient had AD without considering other possibilities or incorrectly believed that a scan had been done previously. Fortunately, such diagnostic errors are becoming less common.

CT or MRI is needed when disruptive behavioral or personality changes occur de novo in middle or late adulthood. Frontal mass lesions often cause dementia and behavioral disturbance with few obvious focal neurological signs, so patients may not be scanned following early symptoms. Alternatively, behavioral symptoms in these patients initially may have been misinterpreted as purely psychiatric and brain imaging considered unnecessary.

Mass lesions are especially likely when dramatic dementia symptoms develop over a period less than a year; this situation warrants a particularly diligent review of imaging results. Although it may seem obvious that a glioma, central nervous system lymphoma, or subdural hemorrhage can cause rapidly evolving cognitive problems, it is

sometimes very difficult to obtain a consistent or accurate history about the timing of symptom onset.

Is There Cerebrovascular Disease?

Stroke and other cerebrovascular diseases are common causes of cognitive impairment and major reasons for obtaining structural neuroimaging in dementia evaluations. Although physicians traditionally seek a single cause of dementia, cerebrovascular disease frequently contributes to the severity of dementia when another dementing disease also is present. Mixed dementia involving both AD and vascular disease becomes increasingly common with age and is an increasing public health concern as the population becomes older (Langa et al. 2004). Indeed, recent evidence suggests that mixed dementia is the most common cause of dementia in a community sample (Schneider et al. 2007).

Structural imaging, particularly MRI, is quite sensitive to cerebrovascular disease, so the major clinical challenge is to determine the significance of lesions that are found. Approximately 30% of elderly people have silent lacunar and cortical infarcts without clinical manifestations (Longstreth et al. 1998). Ideally, clinical relevance can be determined by correlating symptoms with the timing and location of the lesions. For example, in a demented patient with prominent language disturbance, vascular lesions would be expected to involve predominantly the left hemisphere. Careful review of all imaging data and a comparison of findings with different MRI sequences increase the sensitivity of identifying vascular lesions and estimating their age (see Figure 6–1). Nevertheless, relating imaging abnormalities with dementia can be difficult. History may be inadequate, and strokes are often asymptomatic (Price et al. 1997; Vermeer et al. 2002). Substantial motor and sensory recovery may obscure the signs of stroke by the time dementia is evaluated. Furthermore, the severity of dementia may preclude a detailed neurological examination, making it impossible to identify subtle deficits.

The extent of vascular lesions is critical to their clinical relevance and should be fully described as part of image interpretation. A larger number of strokes and more extensive white matter abnormalities increase the probability of causing dementia. Too often clinical reports fail to distinguish minimal from extensive and confluent white matter abnormalities. The high sensitivity of MRI to changes in water content leads to overestimates of the clinical significance of deep white matter hyperintensities. White matter abnormalities are common in the elderly and should be evaluated critically because not all are pathological (Fazekas et al. 1993). Enlarged perivascular spaces cause increased signal on T_2-weighted images but can be distinguished by low signal with FLAIR imaging (Figure 6–2). Neurodegenerative disease can cause white matter abnormalities from Wallerian degeneration and be indistinguishable from small vessel disease. Although the extent of white matter hyperintensity required for clinical significance is uncertain, one consensus group concluded that involvement of at least 25% of white matter was necessary for a clinical diagnosis of vascular dementia (Román et al. 1993).

Location of vascular lesions is also important. Even small thalamic infarcts can cause cognitive impairment (Mungas et al. 2001). Likewise, cognition may be negatively affected when white matter hyperintensities involve cholinergic projection pathways (Bocti et al. 2005; Selden et al. 1998). Cholinergic fibers originate in the nucleus basalis of Meynert and fan out as they ascend following a medial cingulate gyrus pathway and a lateral pathway that proceeds through the external capsule and claustrum into the centrum semiovale adjacent to the gray-white junction (see Figure 6–3).

Evidence of cerebrovascular disease on neuroimaging is insufficient to exclude AD. Alzheimer pathology is often the primary factor for cognitive decline in older individuals with concurrent cerebrovascular injury (Fein et al. 2000), and approximately 30% of patients with AD at autopsy also have evidence of stroke (Gearing et al. 1995). When an individual has extensive vascular lesions, AD can be identified confidently when gradual cognitive decline occurs without change in vascular lesions. Gradient echo MRI showing cortical microhemorrhages typical of cerebral amyloid angiopathy also provides indirect evidence of AD (Viswanathan and Chabriat 2006).

Although MRI is best for identifying vascular lesions, positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG-PET) can help determine the cognitive consequences of these lesions. Stroke often causes metabolic abnormalities that are more extensive than structural lesions because of the loss of distant efferent nerve terminals. For example, a stroke damaging only the thalamus can cause ipsilateral cerebral cortical and contralateral cerebellar hypometabolism, reflecting the location of thalamic pathways (Pappata et al. 1990). These remote metabolic effects are clinically significant, and their localization reflects the types of cognitive deficits observed. Cerebral cortical hypometabolism is the best predictor of whether subcortical lacunar stroke will cause dementia (Kwan et al. 1999).

Is There Ventricular Enlargement?

Ventricular enlargement can be an important indicator of a dementing disease, particularly if the disease is progressive. The presence of ventricular enlargement often is determined subjectively, but a simple alternative is to calcu-

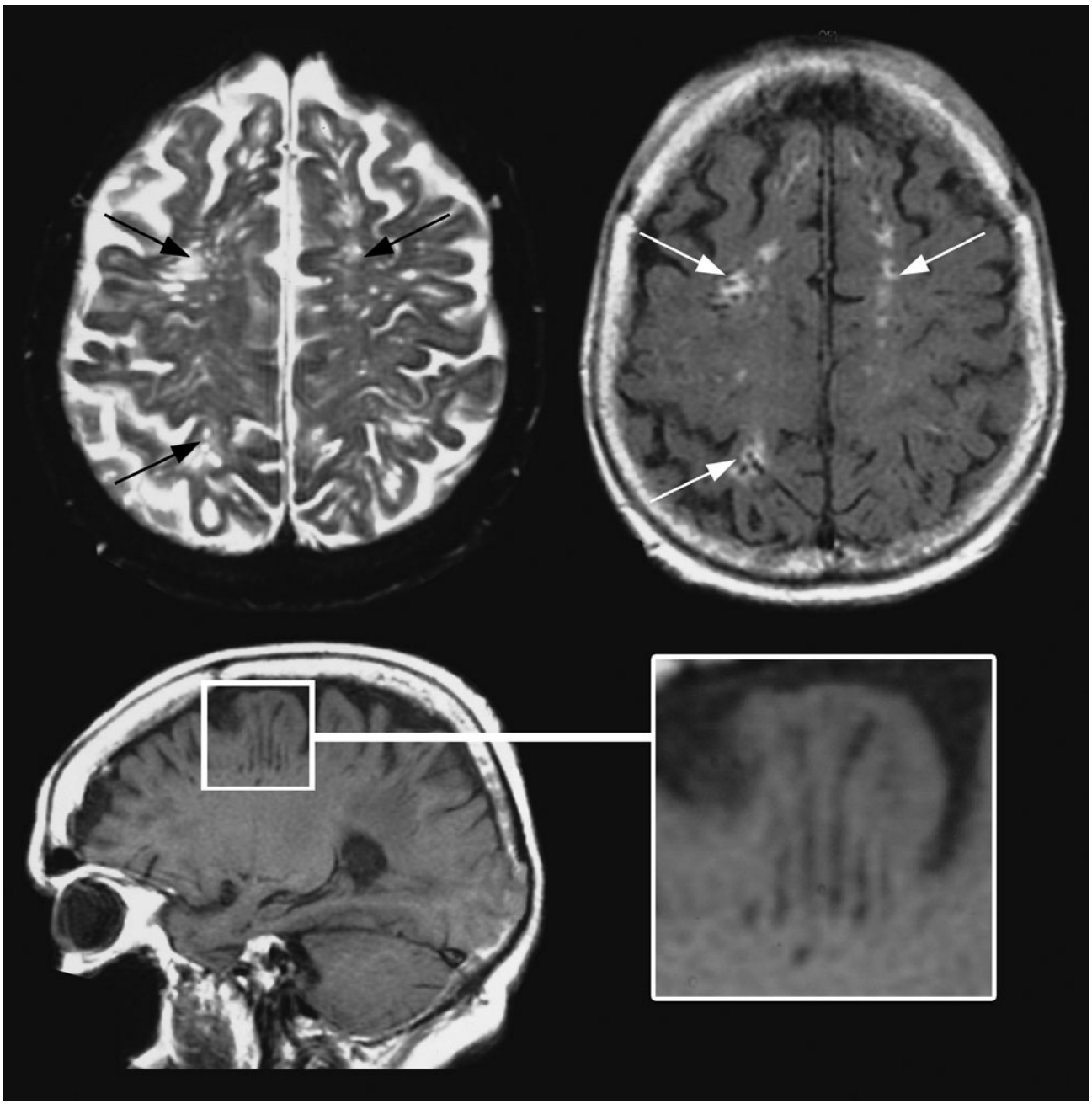

FIGURE 6–2. White matter hyperintensities due to enlarged perivascular spaces.
A T_2-weighted image (top row, left) shows multiple areas of increased signal in the white matter. Although similar to white matter changes seen in chronic small vessel disease, these have a linear pattern, and a fluid-attenuated inversion recovery (FLAIR) magnetic resonance image (top row, right) reveals that many of these hyperintensities have a central area of low signal due to suppression of cerebrospinal fluid in perivascular spaces (arrows). Distinct features also are apparent in T_1-weighted sagittal images (bottom row). Perivascular spaces are linear, running perpendicular to the brain surface following penetrating vessels (inset on right). Areas of decreased signal in posterior periventricular areas (inset on left) have a patchy distribution characteristic of small vessel disease.

late the ratio of the maximal width of frontal horns to the maximal width of the inner skull, which normally is <0.30. Ventricular enlargement can be caused by abnormalities in CSF flow or loss of brain volume (hydrocephalus ex vacuo). Disorders of CSF dynamics are uncommon causes of dementia but are reliably identified with CT and MRI. Both obstructive hydrocephalus and communicating hydrocephalus increase intracranial pressure, and patients present with headache and cognitive deficit. In obstructive hydrocephalus, the ventricular system balloons prox-

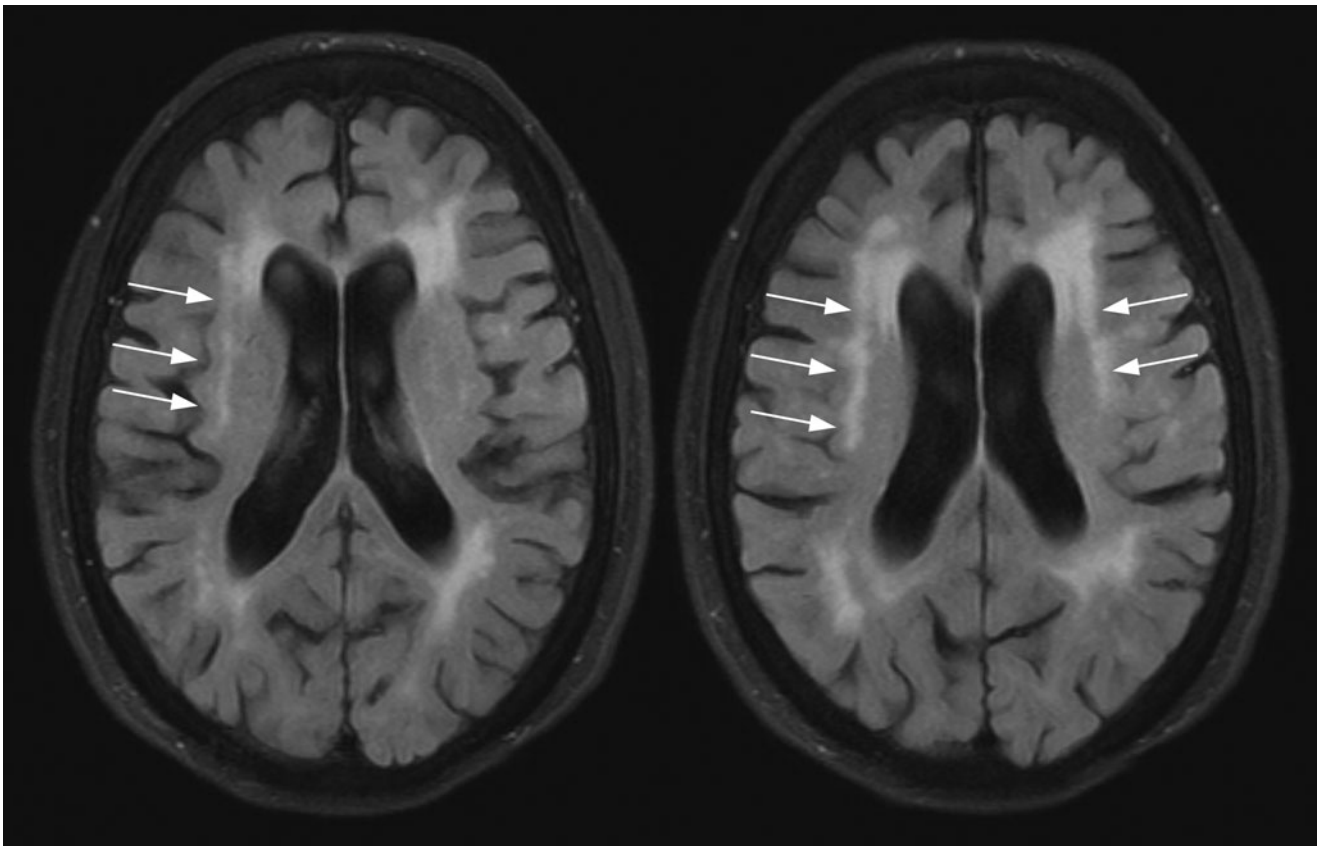

FIGURE 6–3. Critically located white matter hyperintensities.
The location of white matter abnormalities in this 75-year-old woman likely explains her mild memory deficits. Transaxial fluid-attenuated inversion recovery (FLAIR) scans show linear hyperintensities parallel to the margin of the gray-white junction coinciding with the distribution of ascending cholinergic fibers in the extreme capsule (arrows). The scans also show "capping" of the frontal and posterior horns of the lateral ventricles, as often observed in cognitively normal individuals and of less clear clinical significance.

imal to blockage of CSF flow. This obstruction commonly occurs at the cerebral aqueduct, causing disproportionate enlargement of third and lateral ventricles. Aqueductal flow of CSF can be measured precisely with MRI, allowing detection of even partial obstruction. MRI also can identify changes in periventricular brain water due to transependymal flow of CSF.

Structural imaging is essential in identifying normal pressure hydrocephalus, which causes the classic triad of mild dementia, gait apraxia, and urinary incontinence and which responds to ventricular shunting (see Table 6–3). Ventricular CSF flow is unobstructed in normal pressure hydrocephalus, so all ventricles are similarly enlarged. Many imaging criteria have been proposed as possible predictors of response to ventricular shunting, but none has been found reliable (Relkin et al. 2005). The major challenge is to demonstrate that ventricular enlargement is not entirely attributable to cerebral atrophy. Consequently, ventricular enlargement should be disproportionately greater than sulcal enlargement. SPECT imaging is also supportive of the diagnosis of normal pressure hydrocephalus when radionuclide injected after lumbar puncture into the subarachnoid space fails to clear after 48–72 hours.

Ventricular enlargement due to hydrocephalus ex vacuo is a very common feature of AD and other neurodegenerative dementias. In these diseases, all ventricles expand roughly proportionate to enlargement of sulci. Unfortunately, relating the enlargement of ventricular volume to size of sulcal spaces remains a purely subjective determination. However, when sulci are prominent, loss of brain volume is the likely cause of ventricular enlargement and warrants further analysis to determine the pattern of volume loss.

Is There Generalized or Focal Volume Loss?

Loss of brain volume due to atrophy is seen at autopsy in AD and many other neurodegenerative diseases and is the most consistently reported structural imaging abnormality in dementia. The development of CT offered an easy

TABLE 6–3. Structural imaging abnormalities in probable normal pressure hydrocephalus

Required findings

1. Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evan's index >0.3 or comparable measure)
2. No macroscopic obstruction to cerebrospinal fluid flow
3. At least one of the following:
   a. Enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy
   b. Callosal angle of 40 degrees or more
   c. Evidence of altered brain water content, including periventricular signal changes on computed tomography and MRI not attributable to microvascular ischemic changes or demyelination
4. An aqueductal or fourth ventricular flow void on MRI

Other findings considered supportive

1. A brain imaging study performed before onset of symptoms showing smaller ventricular size or without evidence of hydrocephalus
2. Radionuclide cisternogram showing delayed clearance of radiotracer over the cerebral convexities after 48–72 hours
3. Cine MRI study or other technique showing increased ventricular flow rate
4. A SPECT-acetazolamide challenge showing decreased periventricular perfusion that is not altered by acetazolamide

Note. MRI = magnetic resonance imaging; SPECT = single photon emission computer tomography.
Source. Adapted from Relkin et al. 2005.

way to look for brain atrophy in living patients, but initial diagnostic studies were disappointing. It quickly became clear that the age of an individual was a significant determinant of brain volume and had to be taken into consideration. Brain atrophy on average was greater in Alzheimer patients than in cognitively normal elderly subjects of similar age, but significant overlap between individuals limited the diagnostic value of brain atrophy (Gado et al. 1982).

The decline in brain volume with age continues to be a major challenge. Visual interpretation based on the subjective judgment of whether global brain volume is age appropriate varies considerably from one observer to another, is inconsistently applied, and is unreliable. When serial scans are available, diffuse progressive enlargement of CSF spaces over a year or two is easier to identify and suggests AD (Luxenberg et al. 1987). However, for diagnostic purposes, repeated scans add relatively little information to changes in cognition observed over the same time interval. Quantitative and focused approaches are more reliable. One method is to measure total brain volume using scans with uniform characteristics in all three dimensions. A second method is to consider the volume of specific brain regions commonly affected in neurodegenerative diseases.

Typical clinical MRI studies acquire images that have greater resolution in one plane than others to increase signal-to-noise ratio and often have gaps to speed imaging time. However, it is possible to acquire isovoxel images consisting of image elements that are contiguous and of equal size in all dimensions. Isovoxel images permit better delineation of boundaries between CSF, brain, and skull, and thus more accurate measurement of brain volume. Voxel-based morphometry, a computer-assisted approach, is able to distinguish groups of Alzheimer patients and nondemented individuals, and even patients with mild cognitive impairment (Chételat et al. 2002; Frisoni et al. 2002). However, the diagnostic sensitivity and specificity of this approach in individual patients have not yet been studied adequately to recommend its clinical adoption.

Changes in the volume of specific brain regions can be determined reliably with both subjective and quantitative methods. Pathology is so localized in some dementing diseases that focal atrophy often is easily recognized, especially when symptoms are severe. Caudate atrophy is characteristic of Huntington disease and is most evident with coronal images. Progressive supranuclear palsy (PSP) causes midbrain and pontine atrophy, which is frequently apparent on sagittal MRI and can be used to distinguish it from other parkinsonian syndromes (Cosottini et al. 2007). If focal atrophy is evident, it can help confirm a suspected diagnosis, but sensitivity may not be high early in the course of the illness. Because brain size varies significantly with gender and age, these two factors need to be taken into account, particularly when evaluating the significance of quantitative volume measures.

The earliest pathological changes in AD occur in the entorhinal cortex, amygdala, and hippocampus (Braak and Braak 1991). Consequently, it is not surprising that AD causes medial temporal volume loss, which is apparent on MRI scans. Coronal views best visualize the hippocampus and should be obtained routinely in the evaluation of dementia (see Figure 6–2). The resolution of MRI also allows assessment of specific structures within the

medial temporal lobe. Individual medial temporal structures can be outlined manually with good reliability, but this procedure is very tedious and time-consuming and has little clinical applicability. Several automated methods for assessing medial temporal volumes have been developed, but none has been widely adopted, and multicenter validation studies are still needed. Fortunately, hippocampal size is readily apparent on coronal MRI scans, and several studies have found that visual assessment has good sensitivity and specificity in distinguishing AD from normal aging (Scheltens et al. 2002). For example, one qualitative 0–4 scale using rating anchors based on the width of the choroid fissure, width of the temporal horn, and height of the hippocampus achieved specificity of 90%, although at this level sensitivity was only 41%. Medial temporal lobe atrophy also can help identify which patients with mild cognitive impairment will progress to dementia (Visser et al. 2002).

Frontotemporal dementia (FTD) also causes focal atrophy, particularly involving the superior frontal and anterior temporal cortex (Boccardi et al. 2003). Sometimes focal atrophy in these regions is evident on visual assessment. However, the sensitivity and specificity of this finding in individual patients has not been determined, and it is unclear how frequently focal atrophy is obvious at the time of initial assessment. Because the volume of brain regions varies considerably among individuals, focal abnormalities are more clearly pathological when they become more evident over time (see Figure 6–4). Automated measurement of frontal and temporal volume and more recently available measurements of cortical thickness show distinctive abnormalities that correspond to clinical FTD syndromes (Du et al. 2007). In patients with progressive nonfluent aphasia, atrophy is asymmetric, primarily involving language regions (Gorno-Tempini et al. 2004). Quantitative measures of focal atrophy distinguish groups of FTD patients, AD patients, and cognitively normal individuals from each other. It is important to note that FTD also causes hippocampal and amygdalar atrophy (Boccardi et al. 2002, 2003). Consequently, medial temporal atrophy is probably an unreliable way to distinguish AD and FTD.

Molecular Neuroimaging

Molecular neuroimaging probes brain biochemistry by revealing the distribution of tracer quantities of radioactive-labeled drugs designed to participate in metabolism, interact with enzymes and transporters, occupy cellular receptors, or bind cellular and extracellular proteins. Molecular imaging can assess the characteristic biochemical signatures of dementing diseases as they evolve throughout the course of an illness. These methods are powerful but complex. Each tracer has unique properties described with a mathematical equation reflecting a "kinetic model" used to interpret counted emissions. Developing optimal synthesis methods, assessing the applicability of kinetic models, and performing necessary validation studies for clinical application often can take a decade or more to complete. As a consequence, only a few of the many potential molecular imaging strategies have reached clinical practice. Molecular imagin methods to measure cerebral blood flow and metabolism usually are equivalent in dementing illnesses and are the most established molecular imaging methods. Dopaminergic and amyloid imaging also have great clinical promise for dementia care.

Choosing Between PET and SPECT

The fundamental difference between PET and SPECT is the radioactive isotopes used in the two methods. Different instrumentation and acquisition algorithms are required to develop optimal images from positron-emitting and gamma-emitting tracers. Radiopharmaceuticals are valuable when they share the same properties as the substances labeled. The positron-emitting isotopes primarily used in PET (fluorine 18 and carbon 11) are much easier to insert into drugs and naturally occurring substances without altering biological activity than are the large, single photon-emitting isotopes commonly used in SPECT (technetium 99m and iodine 131). Therefore, interpreting and developing quantitative tracer kinetic models is much easier for PET than for SPECT. Furthermore, because positron annihilations produce two gamma rays oriented in opposite directions, PET inherently provides more accurate localization and better spatial resolution than does SPECT, which relies on single photon (gamma) emissions.

These theoretical differences have practical importance. The most commonly used SPECT tracers measure cerebral perfusion, whereas the most commonly used PET tracers measure glucose metabolism. Although glucose metabolism usually parallels cerebral perfusion, glucose uptake is more closely linked to neuronal activity. Consequently, the diagnostic accuracy of PET is superior to SPECT in differentiating AD from vascular demenia (Messa et al. 1994). In the past, SPECT has been more widely used than PET because of better reimbursement and broader availability. However, now that PET is becoming widely available and more frequently reimbursed by insurers, the technical advantages mean that PET likely will gradually replace SPECT in dementia evaluations. The subsequent discussion of molecular imaging, therefore, focuses primarily on PET.

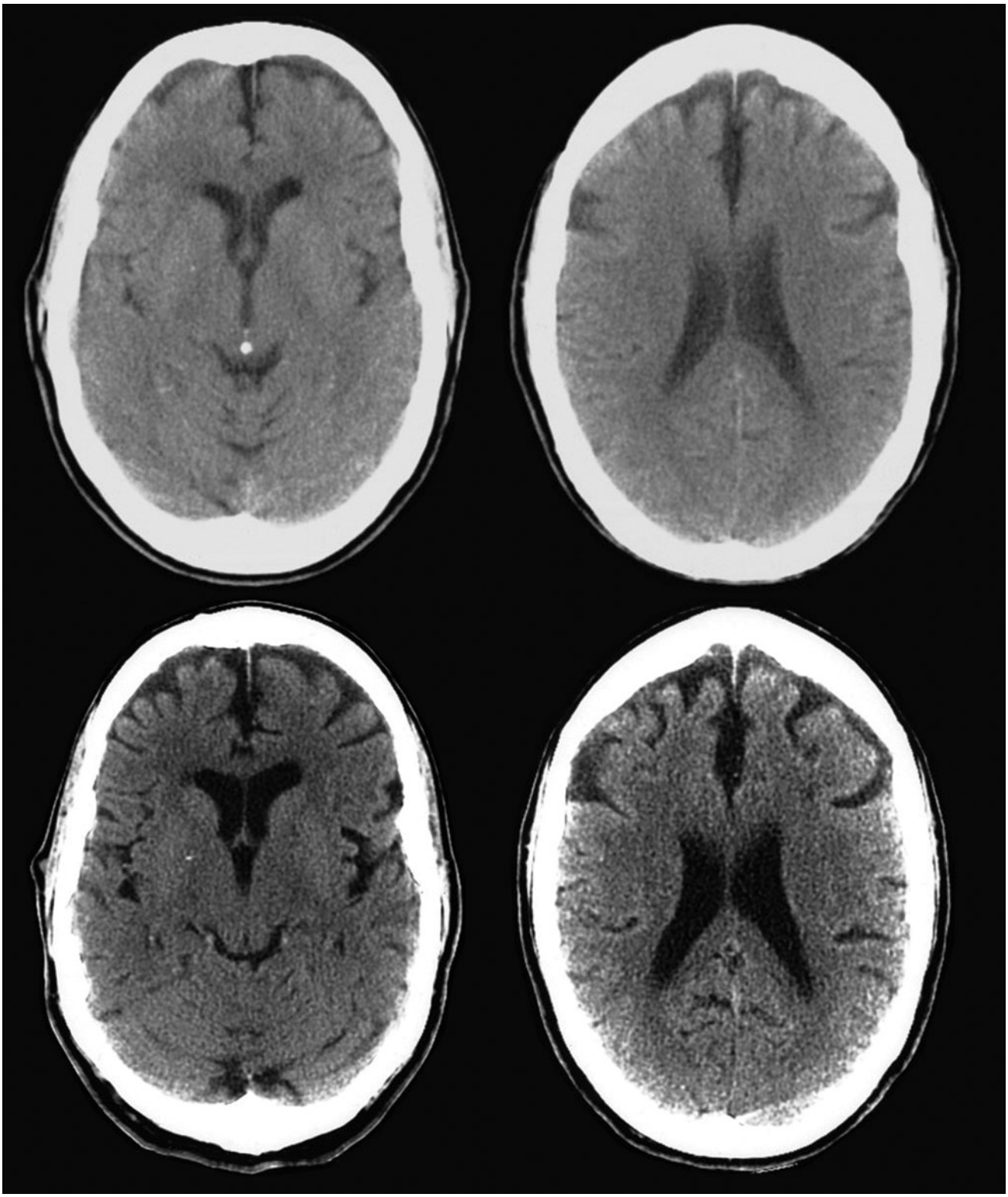

FIGURE 6–4. Progressive focal atrophy.
This woman had memory problems that were first noticed shortly after a minor automobile accident 2 years before her initial assessment at age 84 years. Sulci in the frontal cortex were somewhat more prominent in her initial scan (top row) but were considered to be of uncertain significance and perhaps due to her previous head injury. When her memory deficits remained mild and symptoms failed to progress as expected, another scan was obtained 6 years later (bottom row). Atrophy was progressive and clearly predominant in frontal regions bilaterally. On reevaluation, it was evident that her major disability was due to a change in her personality and profound apathy rather than memory loss, symptoms that are consistent with frontotemporal dementia.

Technical Considerations

Changes in the biological processes measured with molecular imaging occur at the cellular level and can be independent of structural change or reflect structural changes. Consequently, results from CT or MRI are critical for accurately interpreting molecular imaging scans. Many PET scanners now incorporate a CT scanner to help meld structural and molecular images. Unlike structural imaging studies, interpretation of PET and SPECT scans must take into account many factors that can affect the activity and distribution of radioligands. For example, cerebral blood flow and metabolism are affected by patient medication, ambient room conditions, patient attributes such as open or closed eyes, and perhaps the patient's thoughts. Both current and recent medication use may affect the binding of neurotransmitter ligands. Thus, for molecular imaging, the conditions during scanning and medication use must be carefully recorded and controlled.

To decrease subject-to-subject variability, molecular imaging data are commonly "normalized," or adjusted by comparison to an average value in an image or a specified brain region. When this is done, one cannot determine the absolute rate of biochemical reactions, only the value in one brain region relative to another. Nevertheless, the relative distribution of radiotracers has proven adequate for evaluating most disease changes. For glucose metabolism in dementia, there is no ideal region for normalization, but the pons seems to be best suited because pontine glucose metabolism is best preserved in AD (Minoshima et al. 1995).

Diagnostic Questions Most Relevant to Molecular Neuroimaging

What Is the Pattern of Cerebral Hypometabolism?

Glucose is normally the brain's sole energy source, and glucose uptake primarily mirrors synaptic activity (Mata et al. 1980). FDG-PET images reflect brain activity over the 20–30 minutes following radioisotope injection. Therefore, these images can be used to examine a patient's responses to a task performed repeatedly over this uptake phase of the study. However, for clinical studies, individuals usually are asked to rest quietly in a darkened room. In cognitively normal individuals, cerebral metabolism is greatest in the basal ganglia, thalamus, cerebellum, and cerebral cortex; lower in the brainstem; and lowest in white matter (see Figure 6–5). Glucose metabolic rates in the cerebral cortex are reasonably uniform. When eyes are left open, the visual cortex is activated and has higher glucose uptake.

FDG-PET is a sensitive indicator of the distribution of neuronal damage and synaptic failure. Images represent brain activity. Even though clinicians would profit from asking themselves what the pattern of hypometabolism is in every demented patient they encounter, FDG-PET is not always needed. The distribution of hypometabolism usually can be inferred accurately from the patient's history, examination, and relative cognitive deficits. Dementing diseases cause a global decline in glucose hypometabolism, with characteristic and distinctive patterns of regional predominance that evolve along with symptoms and reflect the selective vulnerability of different areas of the brain (see Table 6–4).

Although the underlying disease determines the overall pattern of hypometabolism, individual differences in the regional intensity of the pattern are consistent with individual differences in clinical symptoms and follow classical principles of neurological localization. For example, patients with prominent language disturbance primarily have hypometabolism in the dominant hemisphere, patients with prominent visuospatial disturbance primarily have hypometabolism in the nondominant hemisphere, and patients with behavior disturbance have frontal hypometabolism. The observation that neuronal activity, as measured by cerebral metabolism, correlates with symptoms makes sense. What underlies brain function is the amount and effectiveness of neuronal activity, rather than simply the presence or loss of nerve cells. While theoretically inefficient brain activity caused by futile neuronal discharges or use of circuitous pathways could occur in dementia, these mechanisms would increase glucose metabolism and thus appear not to play a major role. Consequently, although the efficiency of neuronal activity is difficult to determine, decline in synaptic activity, rather than neuronal inefficiency, appears to account for symptoms of dementia and is more consistent with the hypometabolism observed with FDG-PET. Metabolic imaging may be even more reflective of patient symptoms than is pathological examination, which is unable to elucidate all of the physiological consequences of brain injury. Pathological hallmarkers identified microscopically have uncertain effects on neuronal function, and the distribution of damage throughout the brain is difficult to delineate even at autopsy.

As with all imaging, FDG-PET is most helpful when used to answer specific questions after the differential diagnosis has first been narrowed with a careful history and examination. The most established clinical use of FDG-PET is to distinguish AD from FTD. Medicare and most insurance companies now reimburse FDG-PET scans ob-

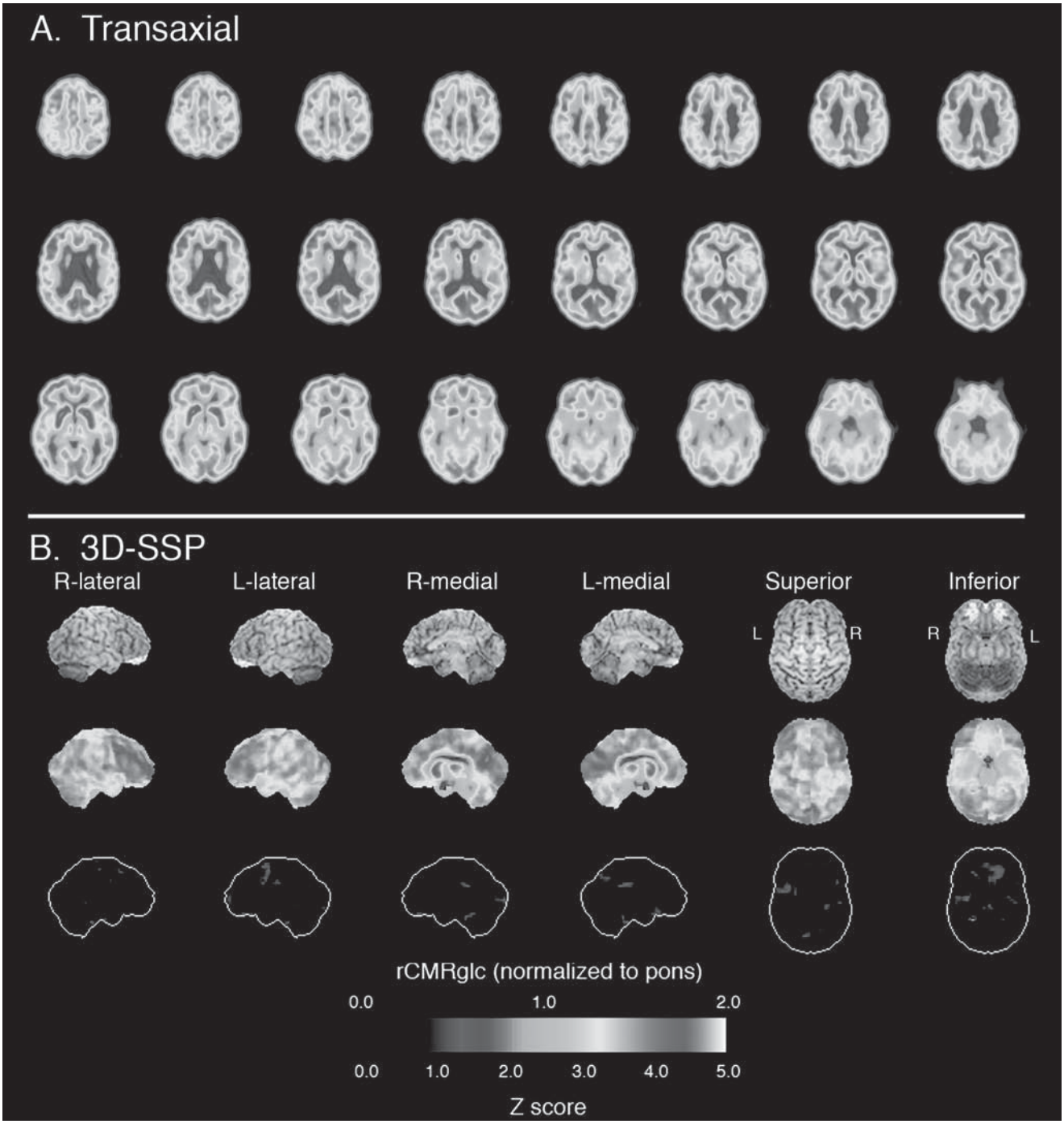

FIGURE 6–5. Fluorodeoxyglucose positron emission tomography (FDG-PET) image in a cognitively normal elderly individual. *(See color plate 1)*

FDG-PET scans produce up to 128 transaxial images, here truncated to the most relevant brain slices for easier display (A). Relative rates of glucose metabolism, in this case relative to pons, are displayed using a color scale shown below the images, with hotter colors representing higher rates of glucose metabolism. Analysis software programs allow scan data to be summarized and displayed in uniform space (B), permitting direct comparison of scans from different individuals. One such program, three-dimensional stereotactic surface projection (3-D SSP), displays scan data from six perspectives, illustrated in a reference image of the brain surface (B, top row). Metabolism relative to pons (B, row 2) is shown using the same color scale as in the transaxial images. A statistical map also can be constructed (B, row 3), showing the *Z*-score of surface pixels in this scan compared to 27 cognitively normal elderly people. Normal individuals have a relatively uniform and high metabolic rate throughout the cerebral cortex. In this case, there are no areas of the brain showing significant reductions in metabolic rate.

TABLE 6–4. Typical patterns of regional cerebral glucose metabolism in common dementing diseases

Disease	Pattern of glucose hypometabolism
Alzheimer disease	Symmetric or asymmetric bilateral temporoparietal and posterior cingulate; lesser frontal association cortex; sparing of primary sensorimotor and visual cortex
Vascular dementia	Multifocal cortical and subcortical, correlating with structural imaging lesions
Parkinson disease with dementia and dementia with Lewy bodies	Symmetric or asymmetric bilateral temporoparietal, posterior cingulate, and visual cortex; lesser frontal association cortex; sparing of primary sensorimotor cortex
Huntington disease	Caudate nucleus and lesser frontal association cortex
Progressive supranuclear palsy	Caudate nucleus, putamen, thalamus, pons, primarily superior and anterior frontal cortex; sparing of cerebellum
Corticobasal degeneration	Asymmetric frontal, temporal, and parietal cortex and thalamus contralateral to limb apraxia

tained for this indication when diagnosis remains unclear after completion of an otherwise comprehensive evaluation. AD and FTD are easily confused because they both lack distinctive neurological signs and have a similar progressive course. FTD typically causes predominant or disproportionate language deficits, with nonfluent progressive aphasia and semantic dementia (Adlam et al. 2006; Gorno-Tempini et al. 2004; Hodges and Patterson 2007). It also causes prominent behavior disturbance (Neary et al. 2005). Although these symptoms sometimes are distinctive enough to be diagnostic for FTD, these same kinds of symptoms also are frequently seen in AD. Indeed, patients with FTD often meet clinical criteria for AD (Varma et al. 1999).

FDG-PET is often very helpful in differentiating AD and FTD, despite their clinical similarities, because they have starkly contrasting patterns of hypometabolism. Foster et al. (2007) used FDG-PET scans from patients with pathologically confirmed disease to distinguish AD from FTD. In this study, visual interpretation of FDG-PET was based on the simple rule that FTD caused greater hypometabolism in anterior cingulate, anterior temporal, and frontal regions than in posterior cingulate and posterior temporoparietal cortex, whereas AD caused the opposite pattern to occur. After raters received brief training, diagnosis based on FDG-PET had greater interrater reliability (mean kappa=0.78) and diagnostic accuracy than clinical information alone. Furthermore, adding FDG-PET to clinical evaluation increased diagnostic accuracy, with a specificity of 97.6% and sensitivity of 86%, and with a positive likelihood ratio of 36.5 for FTD. FDG-PET was particularly helpful when raters were uncertain of their clinical diagnosis.

FDG-PET has not been as extensively studied in other situations involving considerable diagnostic uncertainty. Nevertheless, performing an FDG-PET scan and applying the current knowledge of how different dementing diseases affect the pattern of hypometabolism can be useful in specific circumstances. FDG-PET provides objective evidence of a neurodegenerative disease when medical history is ambiguous or informants are unavailable or unreliable. The pattern of hypometabolism may reveal important additional information when patients have atypical clinical presentation or when diagnostic features are shared by two or more disorders. Because the patterns of hypometabolism in dementing diseases are complex, further detailed description is warranted.

Cerebral hypometabolism in AD is consistent in its typical sequence of regional involvement but varies in detail from patient to patient just as symptoms in individual patients can vary. Hypometabolism is first seen in the posterior cingulate gyrus (Minoshima et al. 1997). It then spreads to affect the association cortex in the parietal and posterior temporal lobes (see Figure 6–6). Eventually, hypometabolism spreads to involve the prefrontal cortex and most of the brain. Although the relative decrease of metabolism in the posterior association cortex, compared with that in the anterior association cortex, remains throughout the course of AD, this discrepancy becomes harder to recognize as frontal regions become progressively more affected. As the surrounding frontal and parietal association cortex becomes more hypometabolic, the relative preservation of the primary sensorimotor cortex surrounding the central sulcus becomes increasingly evident. The occipital lobe, including the primary visual cortex, also is relatively spared. The caudate, putamen, and thalamus are spared relative to the cerebral cortex but are hypometabolic when compared to those of cognitively normal individuals of similar age (Foster et al. 1988). The cerebellum and brain stem are little affected in sporadic AD (Minoshima et al. 1995).

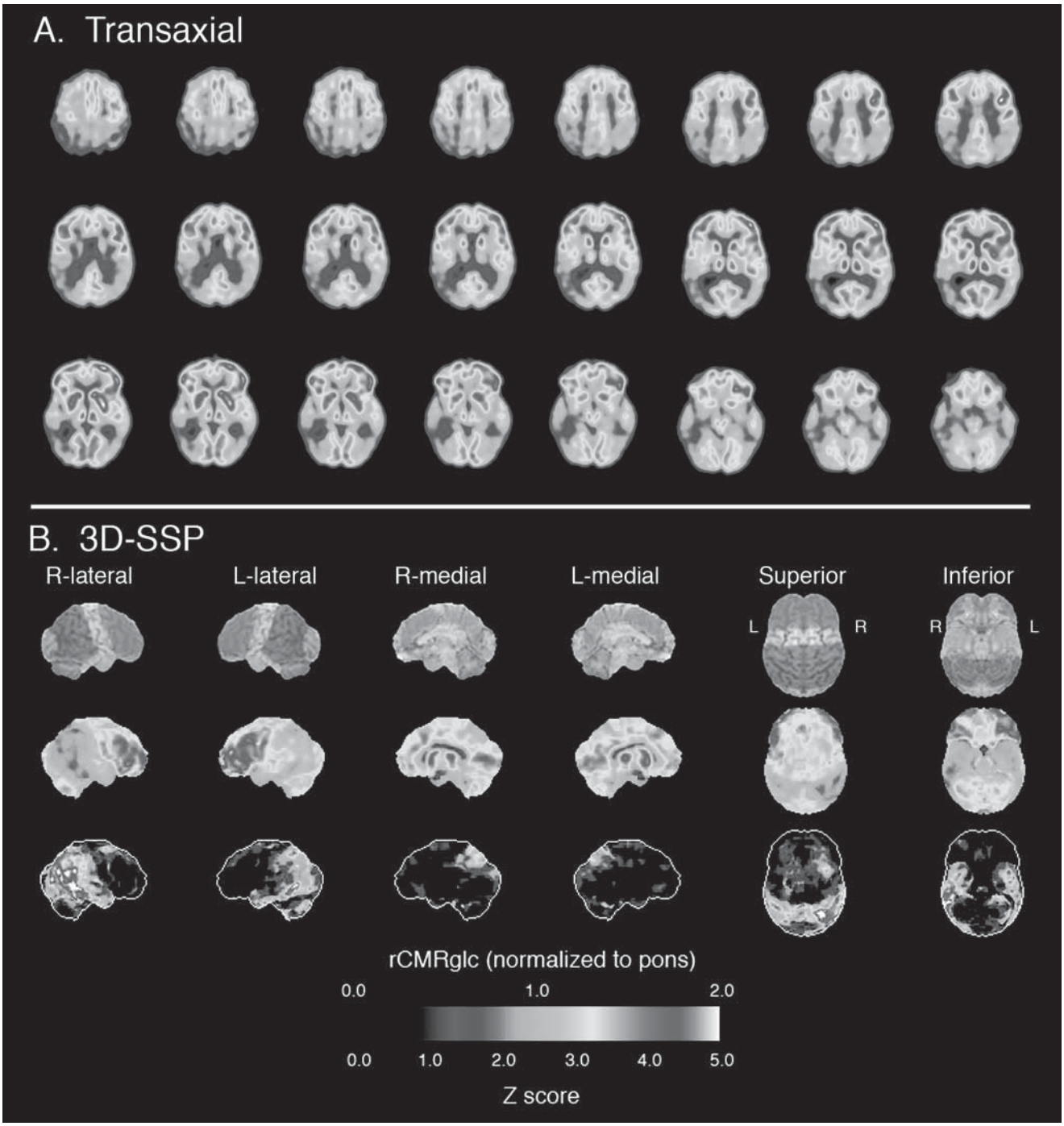

FIGURE 6–6. Fluorodeoxyglucose positron emission tomography (FDG-PET) in a patient with Alzheimer disease. *(See color plate 2)*

Transaxial (A) and three-dimensional stereotactic surface projection (3D-SSP) displays (B) of an FDG-PET scan from a patient with Alzheimer disease are shown. In this case, the reference image of the brain surface (B, top row) has been colored to indicate areas typically most affected in Alzheimer disease (pink=temporoparietal association cortex; orange=posterior cingulate cortex) and frontotemporal dementia (purple=frontal association cortex; blue=posterior cingulate cortex; green=anterior temporal cortex). Alzheimer disease causes glucose hypometabolism predominantly in posterior regions of the cerebral cortex (A; B, row 2). The statistical map (B, row 3) shows that some regions have hypometabolism 5 standard deviations (Z=5) from that seen in 27 cognitively normal elderly individuals. Cerebral metabolism for glucose is shown relative to pons values (rCMRglc).

The initial involvement of the posterior cingulate gyrus in AD is perhaps unexpected because the hippocampus and medial temporal lobe appear to suffer the earliest damage on traditional neuropathological examination. Considerable evidence indicates that metabolic declines are greater in the posterior cingulate cortex and lateral temporal cortex because synaptic projections from the hippocampus and medial temporal cortex are damaged. Neurotoxic lesions in the entorhinal and perirhinal cortices in monkeys cause neocortical hypometabolism (Meguro et al. 1999). Anterior temporal lobectomy performed to treat epilepsy also causes posterior cingulate hypometabolism (Minoshima et al. 1999). Furthermore, hippocampal atrophy correlates with posterior cingulate hypometabolism in AD (Meguro et al. 2001).

Clinical criteria for AD have relatively poor specificity, and misdiagnoses occur in community practice and even at leading academic centers (Becker et al. 1994; Blacker et al. 1994; Mendez et al. 1992). FDG-PET is a promising method to improve AD diagnosis. Visual interpretation of FDG-PET scans has higher diagnostic accuracy than clinical evaluation alone when autopsy diagnosis is used as the gold standard. The diagnostic sensitivity (93%–94%) and specificity (73%–79%) of FDG-PET is better than that of clinical evaluation alone (sensitivities of 79%–85% and specificities of 50%–70%) (Hoffman et al. 2000; Lim et al. 1999; Silverman et al. 2001).

FTD causes glucose hypometabolism predominantly in anterior brain regions, including the frontal cortex, anterior cingulate cortex, and anterior temporal regions (Foster et al. 2005). As symptoms progress, deficits become more pervasive, but anterior regions remain predominantly affected, and primary motor-sensory and visual cortex and posterior association cortex are relatively spared. Several clinical phenotypes of FTD are recognized (see Chapter 12, "Frontotemporal Dementia") and cause corresponding variations in this overall pattern of glucose hypometabolism (Miller et al. 1993). Patients with severe behavior disturbances tend to have predominant right hemisphere hypometabolism, whereas those with progressive aphasia exhibit more hypometabolism in the dominant hemisphere (see Figure 6–7). Hypometabolism in some FTD patients is mostly in the anterior temporal cortex, but in others it is almost entirely limited to the frontal cortex. The reason for these individual variations is not yet understood (Foster et al. 2005).

Dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD) both show a pattern of glucose hypometabolism similar to that in AD, with the added characteristic of occipital hypometabolism, whether or not there is also Alzheimer pathology (Ishii et al. 1998; Minoshima et al. 2001). The cause of occipital hypometabolism remains uncertain. The metabolic similarities of DLB and AD—that is, bilateral temporoparietal and lesser degrees of frontal hypometabolism—are not surprising given the frequent difficulty in clinically distinguishing these disorders. Current clinical criteria for DLB have good specificity but poor sensitivity, and patients with pathologically confirmed DLB often have been misdiagnosed as having AD (Weiner et al. 2003). Imaging with a dopaminergic marker may be particularly valuable in distinguishing AD from DLB (see "Is There Loss of Dopaminergic Neurons?" below), but neuroimaging cannot distinguish DLB from PDD. Perhaps this is not surprising because, although clinical presentation and clinical criteria differ, the pathological findings in these two disorders are indistinguishable.

Distinctive patterns of glucose hypometabolism also have been identified in progressive supranuclear palsy and corticobasal degeneration. In most cases, the characteristic motor symptoms of PSP and corticobasal degeneration are sufficient for diagnosis, but the pattern of hypometabolism is occasionally helpful. FDG-PET findings differ between PSP and DLB and between PSP and PDD even though they have similar abnormalities on dopaminergic imaging. Compared to cognitively normal subjects, patients with PSP have glucose hypometabolism in the caudate nucleus, putamen, thalamus, pons, and cerebral cortex (Foster et al. 1988). Declines of glucose metabolism are most prominent in the superior and anterior portions of the frontal cortex in a manner that is now better understood as causing a pattern typical of tauopathies (see Chapter 12 of this volume). However, glucose metabolism in the cerebellar cortex is normal in PSP. This pattern can be helpful in distinguishing PSP from cerebellar degeneration, both of which have gait ataxia as an early symptom. Corticobasal degeneration is characterized by significant metabolic hemispheric asymmetry, just as the clinical symptoms are typically very asymmetric. Nearly the entire affected hemisphere, including frontal, temporal, and parietal regions, is involved. However, in addition to the asymmetry in the cerebral cortex, ipsilateral thalamic hypometabolism is evident, while the striatum seems relatively spared (Eidelberg et al. 1991). Although corticobasal degeneration, FTD, and PSP are now known to share tau pathology, they have remarkably different clinical symptoms and patterns of glucose hypometabolism.

Because FDG-PET is a measure of synaptic activity, it is reasonable to expect that it is affected early in neurodegenerative diseases. Synaptic loss as an early sign of neurodegenerative disease has been best shown in AD, where synaptic failure precedes axonal loss and neuronal death (DeKosky et al. 1990; Selkoe 2002). When changes in metabolism first appear is unknown, but groups of individu-

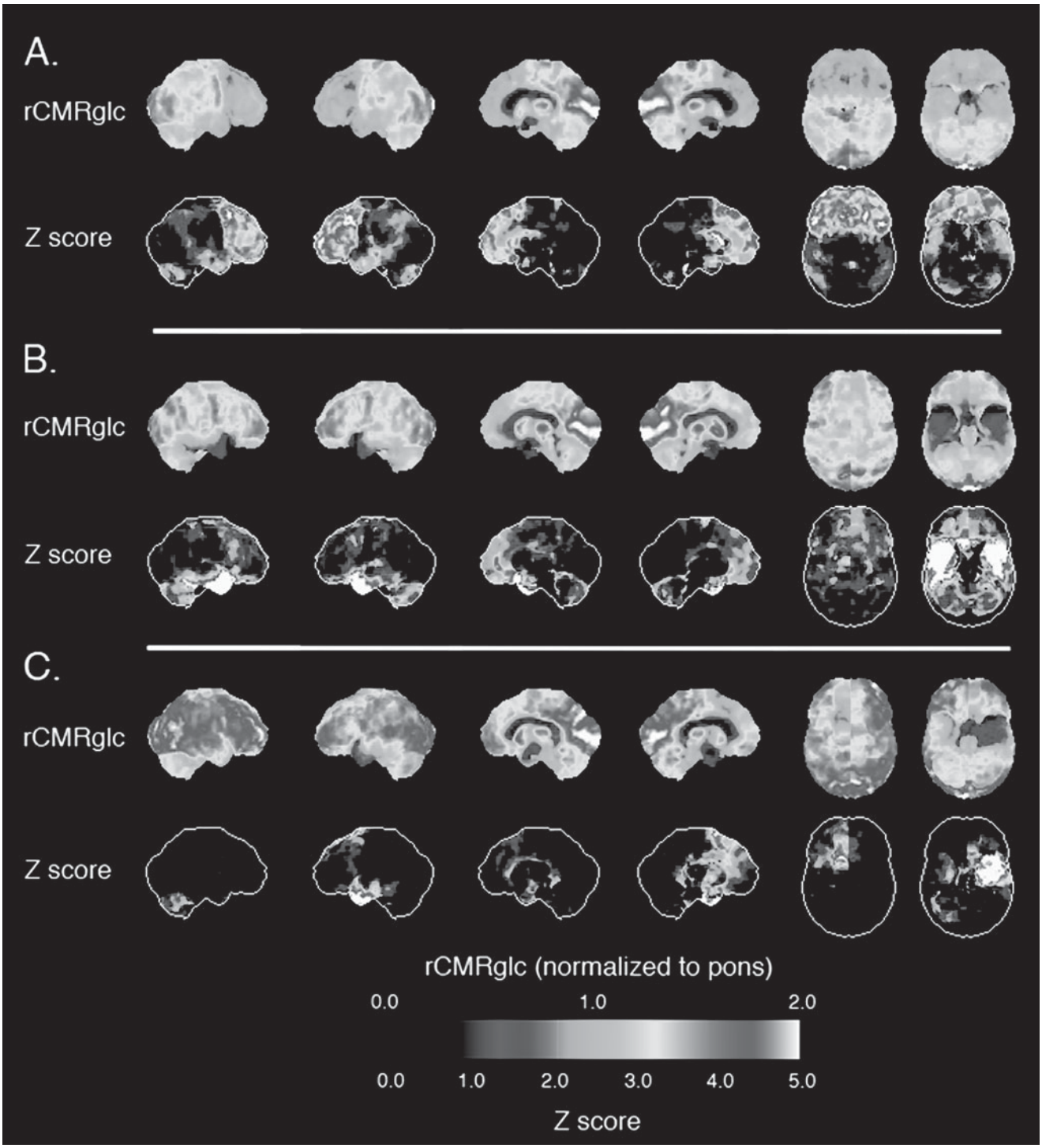

FIGURE 6–7. Fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with frontotemporal dementia (FTD). *(See color plate 3)*

FDG-PET scans from three patients with FTD (A, B, C), displayed as three-dimensional stereotactic surface projection (3D-SSP) glucose metabolic (rCMRglc) and statistical (*Z* score) maps as in Figures 6–5 and 6–6, illustrate the individual heterogeneity of this disorder. FTD causes glucose hypometabolism predominantly in frontal, anterior cingulate, and anterior temporal regions (see Figure 6–6), but its relative severity can vary considerably. Just as FTD causes several clinical syndromes, the pattern of glucose hypometabolism may differ from patient to patient. The cerebral hemispheres can have similar hypometabolism (A, B) or significant metabolic asymmetry (C). Sometimes the frontal association cortex and anterior cingulate gyrus can be the primary sites of hypometabolism (A). In other cases, the anterior temporal lobes are predominantly affected (B, C), with variable involvement of other regions.

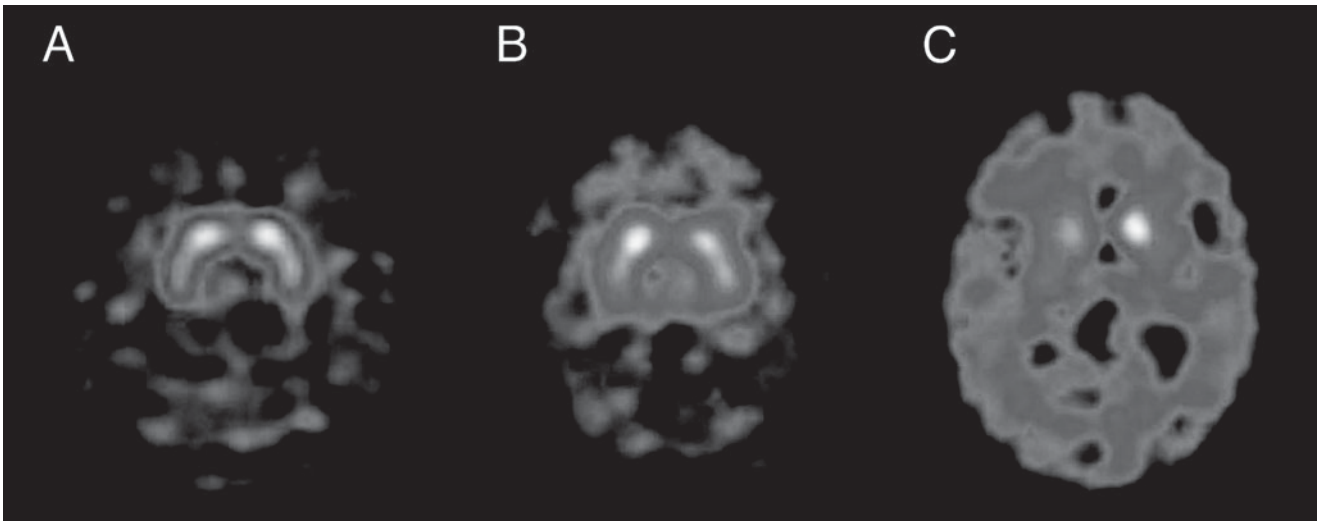

FIGURE 6–8. Dopamine imaging in patients with Alzheimer disease and dementia with Lewy bodies (DLB). *(See color plate 4)*
β-CIT SPECT scans in a cognitively normal individual (A), an 83-year-old patient with Alzheimer disease (B), and an 81-year-old patient who has probable DLB (C). Following an initial uptake phase that primarily reflects cerebral blood flow, static images shown here were obtained reflecting binding to dopamine uptake sites in the striatum. Binding is proportionate to the intensity of "hot" colors. Scans from the normal and Alzheimer disease subjects show a similar comma-like pattern. This is in contrast to the scan in the patient with DLB, which shows a more restricted "full stop" pattern of uptake. In the DLB patient (C), the intensity of the striatum is asymmetric, with greater uptake in the left than in the right, a typical finding in both Parkinson disease and DLB. Uptake in all images is displayed relative to cerebellum because absolute binding rates are not easily calculated in clinical studies. β-CIT = *N*-delta-(fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane.
Source. Images are provided courtesy of GE Healthcare.

als presumed to be at high risk for AD based on apolipoprotein ε4 genotype show metabolic changes long before symptoms are expected, particularly in the posterior cingulate gyrus, where hypometabolism begins in AD (Reiman et al. 1996; Small et al. 2000). Furthermore, several studies have shown that FDG-PET helps distinguish individuals with memory disturbance who later will develop AD. Many nondemented individuals with mild cognitive impairment show a pattern of cerebral glucose metabolism identical to that of patients with AD (see Figure 6–6). Moreover, patients with mild cognitive impairment are much more likely to develop AD over the subsequent few years if they exhibit AD patterns of glucose hypometabolism than if they do not (Anchisi et al. 2005; Berent et al. 1999; Chételat et al. 2003).

Is There Loss of Dopaminergic Neurons?

Dopaminergic function is affected in many dementing illnesses, including DLB, PDD, and PSP. Furthermore, rigidity frequently develops in moderate and severe AD. The presence of parkinsonian features provides important clinical evidence of these disorders, but the sensitivity of clinical diagnosis is relatively low in most series. Molecular imaging provides a more objective and quantitative measure of dopaminergic function. Tracers are available to evaluate the integrity of dopaminergic neurons at several sites. Uptake of dopa, the dopamine precursor, can be measured with [^{18}F]fluorodopa. Radiotracers are available that bind to the vesicular monoamine transporter 2, which is responsible for storage of dopamine in synaptic vesicles, and to the dopamine transporter (DAT), which facilitates reuptake of dopamine into axons (Brooks et al. 2003). These tracers have been widely used in research studies, but none is currently available for clinical use in the United States or Canada. However, the SPECT DAT tracer [^{123}I]β-CIT (*N*-delta-[fluoropropyl]-2beta-carbomethoxy-3beta-[4-iodophenyl]tropane) is approved for clinical use in England and Europe to differentiate DLB from AD. These studies are relatively easy to interpret because, after an initial uptake phase, remaining ligand is limited primarily to the striatum (site of dopaminergic projection axons from the substantia nigra). Both the amount and the morphological shape of binding can be helpful diagnostically, with normal distribution appearing in a comma shape, whereas with loss of dopamine neurons, posterior and caudal binding diminishes, causing a full-stop or circular pattern (see Figure 6–8). In a prospective study of 288 demented patients with and without DLB

who had acceptable [^{123}I]β-CIT scans, diagnostic accuracy, compared to consensus diagnosis based on the scan alone, was 85% for probable DLB, with a sensitivity of 77% and a specificity of 90% (McKeith et al. 2007). This compares favorably to the average sensitivity of 49% for the clinical diagnosis of probable DLB when compared to autopsy diagnosis. Consequently, [^{123}I]β-CIT appears valuable for increasing the detection of DLB (specificity, but not sensitivity, of the clinical criteria for probable DLB is already high). Accuracy and specificity of possible DLB using both clinical and imaging criteria are considerably lower, and autopsy findings still are needed before clinicians can truly know whether imaging dopaminergic deficits in this situation are truly reliable.

As with other molecular imaging studies, a patient's use of drugs must be closely examined when interpreting scans of dopamine function. For example, bupropion and a number of other drugs affect [^{123}I]β-CIT scans. Because short-term use of levodopa or dopamine agonists and antagonists that act on postsynaptic dopamine receptors do not affect the scans, identifying DLB in patients receiving neuroleptic drugs should be possible without knowing for certain that parkinsonian symptoms are spontaneous. However, more study is needed to evaluate the effects of long-term treatment with dopaminergic agonists and antagonists on all ligands used in dopaminergic imaging (Ravina et al. 2005).

In Britain and Europe, [^{123}I]β-CIT scans are also approved to help differentiate Parkinson disease from essential tremor. Usually, the clinical circumstances, including typical features and response to treatment, are sufficient for an accurate diagnosis. Although a positive scan may occasionally help confirm a diagnosis of PDD, it cannot distinguish PDD from PSP or multiple system atrophy. One of the more intriguing opportunities is to improve diagnostic accuracy by assessing regional hypometabolism and dopaminergic function together. Use of a dopaminergic tracer provides an alternate and objective method of determining whether there is nigral pathology, which is always present in DLB. Simultaneous analysis of uptake and receptor binding phases of a dopaminergic tracer might substitute for a separate metabolic scan (Koeppe et al. 2005).

Are There Amyloid Plaques?

Undoubtedly, one of the most exciting developments in dementia imaging is the production of small-molecule radioactive probes for the in vivo assessment of Alzheimer pathology. These probes have generated intense interest, and remarkable progress has been made over a short time in the research necessary for modeling and validation. Both SPECT and PET agents have been proposed for amyloid imaging. Work is furthest along on the positron emitting ^{11}C tracer Pittsburgh compound B (PIB), which is under active investigation at more than a dozen sites. This lipophilic tracer is a derivative of thioflavin-T and easily crosses the blood-brain barrier and appears to bind only fully formed plaques (Klunk et al. 2004; Mathis et al. 2002). A tracer kinetic model for PIB requires only venous access and uses a simple method for analysis (Price et al. 2005). PIB binding is much more evident in the cerebral cortex in patients with AD, whereas binding is similar in white matter and cerebral cortex in cognitively normal individuals (see Figure 6–9). Amyloid imaging complements FDG-PET findings. Increased PIB binding can be seen when FDG-PET scans are normal. Preliminary studies indicate that binding of this tracer is not limited to patients with clinically diagnosed AD. Some elderly individuals who are not demented and some who have DLB also show increased PIB binding consistent with pathological studies (Rowe et al. 2007). The presence of increased PIB binding in nondemented elderly and in patients with mild cognitive impairment raises the question whether these findings will predict later development of AD (Forsberg et al. 2008). Furthermore, PIB binding is seen in some patients with clinically diagnosed FTD, suggesting that these individuals may actually have AD (Engler et al. 2008; Rabinovici et al. 2007). If further validation studies are successful, it may be possible to use amyloid imaging to study the evolution of neuritic plaques and their relationship to dementia symptoms and treatment response.

Other amyloid imaging agents are under active development. The tracer [^{11}C]SB-13, which is similar to [^{11}C]PIB, has been developed and partially validated (Verhoeff et al. 2004). PET amyloid tracers using ^{18}F, which has a longer half-life, also are under development. Another PET ligand, [^{18}F]FDDNP, has a different pattern of binding and appears to image both neurofibrillary tangles and neuritic plaques (Small et al. 2006). It is unclear whether this will have any advantages over imaging amyloid alone, but binding of [^{18}F]FDDNP does appear to increase as symptoms progress.

Special Situations

The causes of dementia that must be considered and the uses of neuroimaging are different when dementia progresses rapidly over a few weeks or months, when it begins before age 60 years, and when it appears to be inherited. Neuroimaging also can be particularly helpful in evaluating symptoms that evolve in the course of a progressive dementia.

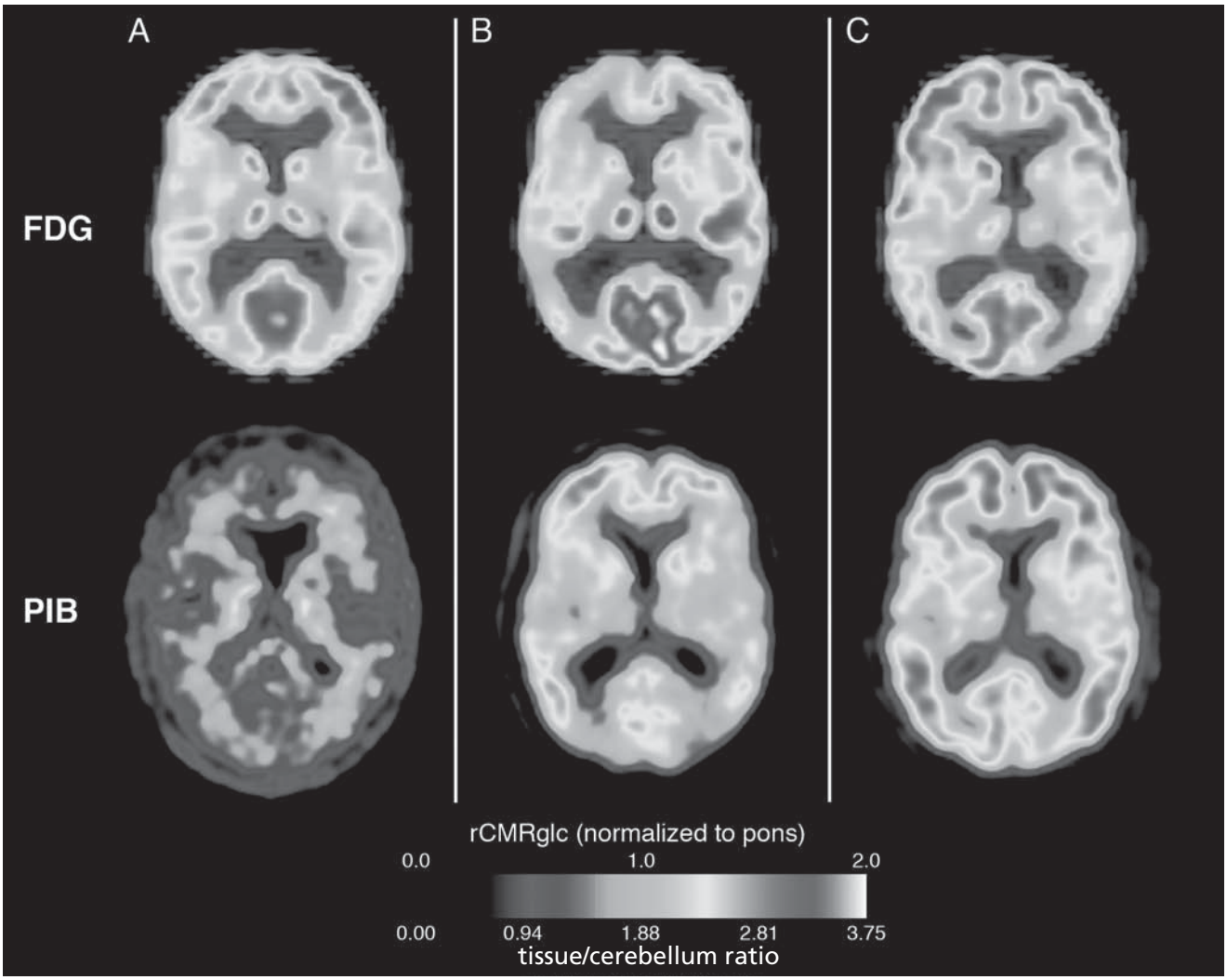

FIGURE 6–9. Amyloid positron emission tomography (PET) imaging. *(See color plate 5)*
Transaxial fluorodeoxyglucose positron emission tomography (FDG-PET) scans (top row) and amyloid PET scans with ^{11}C-PIB (bottom row) from a cognitively normal elderly individual and two patients with Alzheimer disease (AD) are shown, using the color scale shown below the images. The normal subject (A) has a normal distribution of FDG in the cerebral cortex, whereas both AD patients (B, C) have predominant temporoparietal hypometabolism. Hypometabolism is greater in one AD patient (B) than the other (C) and also involves the right frontal cortex. Amyloid binding relative to the cerebellum is primarily evident in the white matter in the cognitively normal subject (A, bottom row). In the two patients with AD, amyloid binding is much greater in the cerebral cortex, nearly obscuring the binding in the white matter. Amyloid binding is not closely correlated with the severity or distribution of glucose hypometabolism. The AD patient with the most pronounced cerebral hypometabolism (B) has less ^{11}C-PIB binding than the other AD patient (C). Glucose metabolism is greatest in the visual cortex, where ^{11}C-PIB binding is not particularly high. Furthermore, there may be high amyloid binding in the frontal cortex (B), even if metabolism is little affected there (C).

Rapidly Progressive Dementia

Structural imaging is essential and MRI is clearly preferable to CT when evaluating a patient with rapidly progressive dementia. The superior sensitivity and flexibility of MRI is often extremely valuable in detecting multiple, small, disseminated lesions due to metastases or vasculitis, and vascular lesions from emboli due to endocarditis, cardiac thrombus, open-heart surgery, or a peripheral venous thrombus reaching the brain through a patent foramen ovale. Quickly identifying these conditions is critical because early treatment often can improve or stabilize the cognitive deficits.

Another advantage of MRI is its ability to detect prion diseases. Creutzfeldt-Jakob disease and other prion diseases very commonly cause focal increased signal on diffusion-weighted imaging, FLAIR, and proton-weighted MRI, and to a lesser extent on T_2-weighted imaging (Finkenstaedt et al. 1996; Na et al. 1999). Diffusion-weighted imaging appears most sensitive. It is important to recog-

nize that CT scans and routine T_1-weighted MRI images may be normal in Creutzfeldt-Jakob disease. Therefore, the clinician may need to specifically request diffusion-weighted and FLAIR images and to focus the radiologist's attention to the suspected regions of interest, because the typical abnormalities of prion disease may not be recognized due to its low prevalence.

MRI diffusion changes are probably caused by gliosis and microscopic spongiform vacuolization. MRI abnormalities in typical, sporadic Creutzfeldt-Jakob disease are most often bilateral and symmetric, with increased signal in the putamen and caudate nuclei (Schroter et al. 2000). The cerebral cortex also can have focal abnormalities that have a distinctive ribbon appearance (see Figure 6–10). By contrast, FLAIR images show diffuse abnormalities in stroke that involve both gray and white matter. The location of MRI changes in Creutzfeldt-Jakob disease can be either symmetric or asymmetric, reflects the distribution of prion pathology, and correlates with patient symptoms (Kropp et al. 1999; Mittal et al. 2002). In new variant Creutzfeldt-Jakob disease, acquired from exposure to bovine spongiform encephalopathy, increased signal typically occurs in the pulvinar of the thalamus (Zeidler et al. 2000). This so-called pulvinar sign has not been reported in sporadic or familial prion disease.

Early-Onset and Familial Dementia

Dementia occurring before the patient is age 60 years requires closer consideration of diseases that are uncommon later in life. Traumatic injury, brain tumors, human immunodeficiency virus (HIV), and other sexually transmitted infections are potential causes. Frontotemporal dementia is nearly as common as Alzheimer disease in this age group. Early-onset dementia, which is often inherited, is another possibility. Some familial dementing disorders have distinctive imaging findings.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) causes progressive dementia beginning in the third to sixth decades of life. This disease may go unrecognized for many years and be first identified only after the typical features are seen on brain scanning. Definitive diagnosis depends on identifying electron-dense inclusions in capillaries on biopsy or a causative mutation in the *NOTCH3* gene on chromosome 19. MRI shows lacunar infarcts and microhemorrhages that become more numerous over time. The most distinctive imaging feature of CADASIL is areas of hyperintensity in the anterior temporal lobes (Figure 6–11). In one study, a characteristic pattern of bilateral hyperintense white matter located directly below the cortical ribbon was found in all 40 patients with CADASIL, even in the youngest (van den Boom et al. 2003).

Familial AD also may have usual clinical and imaging findings. Some presenilin 1 mutations cause spastic paraparesis and can be associated with less dense cotton-wool plaques. In such cases, AD seems very aggressive and may involve areas that are usually spared, such as the primary motor cortex (Moretti et al. 2004). Likewise, some presenilin 1 mutations are associated with cerebellar amyloid plaques. Cerebellar glucose metabolism is usually normal in AD, but in these cases there may be cerebellar hypometabolism (Murrell et al. 2001).

Evolving Symptoms

When dementing diseases progress, imaging can help in understanding the cause of unexpected symptoms. In neurodegenerative diseases, symptoms are expected to evolve gradually and follow a typical course characteristic of each disorder. For example, worsening of memory loss or slow development of more severe language deficit in AD would not be surprising. Sometimes, however, the cause of dementia may be brought into question when the course of a patient's illness differs from that predicted by the clinical diagnosis (see Figure 6–4). In these cases, additional imaging studies are needed so appropriate treatment can be started.

It is impossible to consider all situations in which evolving symptoms warrant neuroimaging, but a few examples should be illustrative. Patients with AD are not expected to develop sudden hemiparesis or aphasia. If this occurs, an MRI is likely to show a cerebral infarct, subdural hematoma, or intracerebral hemorrhage. If apathy, inattention, perseveration, or loss of verbal fluency become more pronounced than memory loss in a patient thought to have AD, then FDG-PET is appropriate. In this case, the correct diagnosis may be FTD instead of AD. FDG-PET showing bilateral temporoparietal hypometabolism or abnormal amyloid imaging may help confirm AD when cognitive deficits worsen in a patient with vascular dementia, even though no new vascular lesions are seen with MRI.

Patients with dementia due to neurological disease almost uniformly have abnormal FDG-PET scans, whereas those with cognitive complaints for other reasons usually have normal scans. FDG-PET scans are abnormal even when symptoms of AD are mild. Thus, a normal pattern of glucose metabolism may provide additional assurance that the initial diagnosis was in error when a patient thought to have AD fails to get worse. FDG-PET also may be useful in differentiating neurodegenerative disease from cognitive impairment due to psychiatric illness,

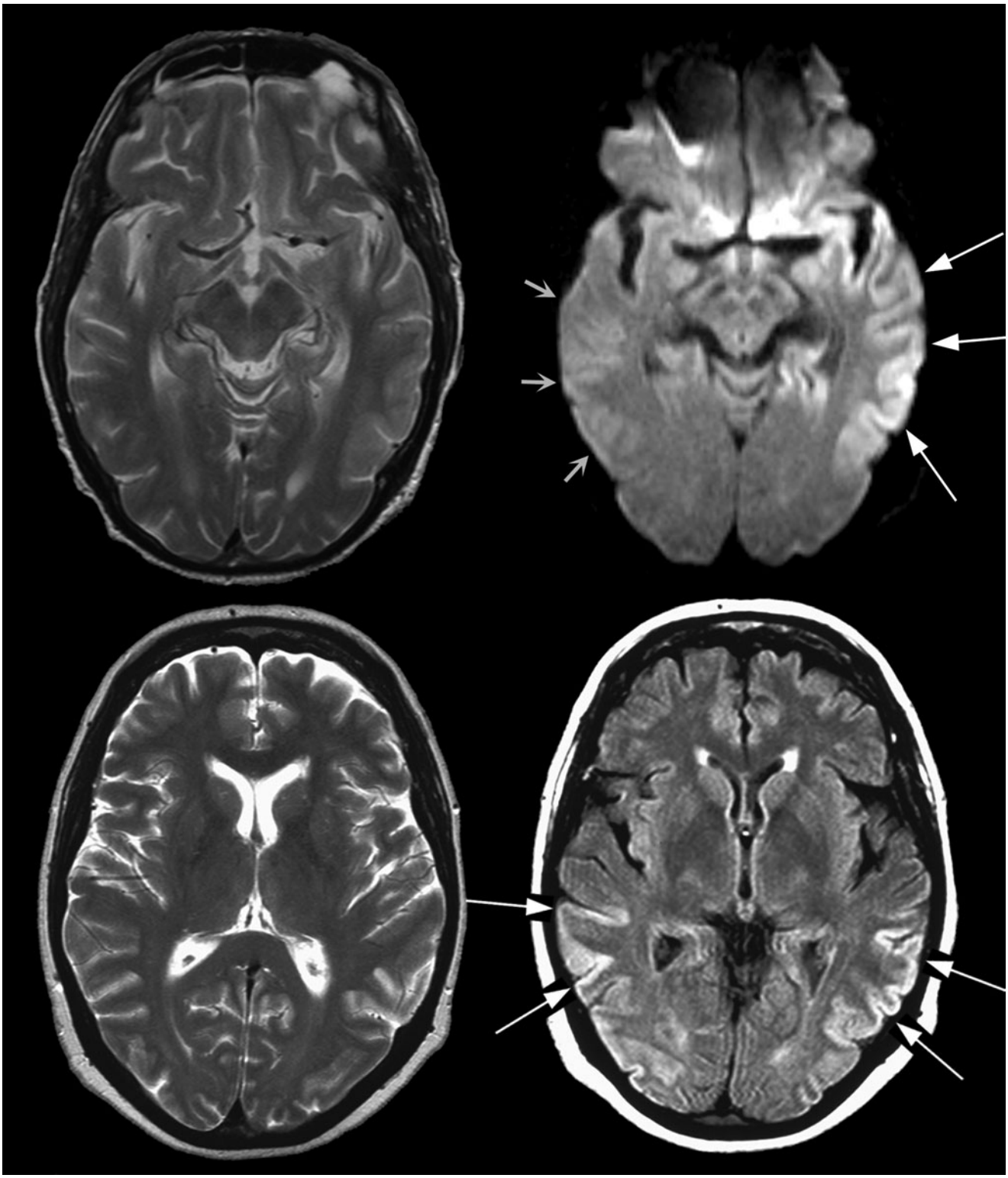

FIGURE 6–10. Magnetic resonance imaging in patients with Creutzfeldt-Jakob disease.
Magnetic resonance images show hyperintensities following the cortical ribbon in two patients with pathologically confirmed Creutzfeldt-Jakob disease. In one patient, a T_2-weighted image (row 1, left) shows no abnormality, whereas the diffusion-weighted image (row 1, right) shows increased signal in the left temporal lobe (large arrows) that is not seen on the right (small arrows). The second patient also fails to show any abnormalities on a T_2-weighted image (row 2, left), although the fluid-attenuated inversion recovery (FLAIR) image shows increased signal in the temporoparietal cortical ribbon bilaterally (large arrows).

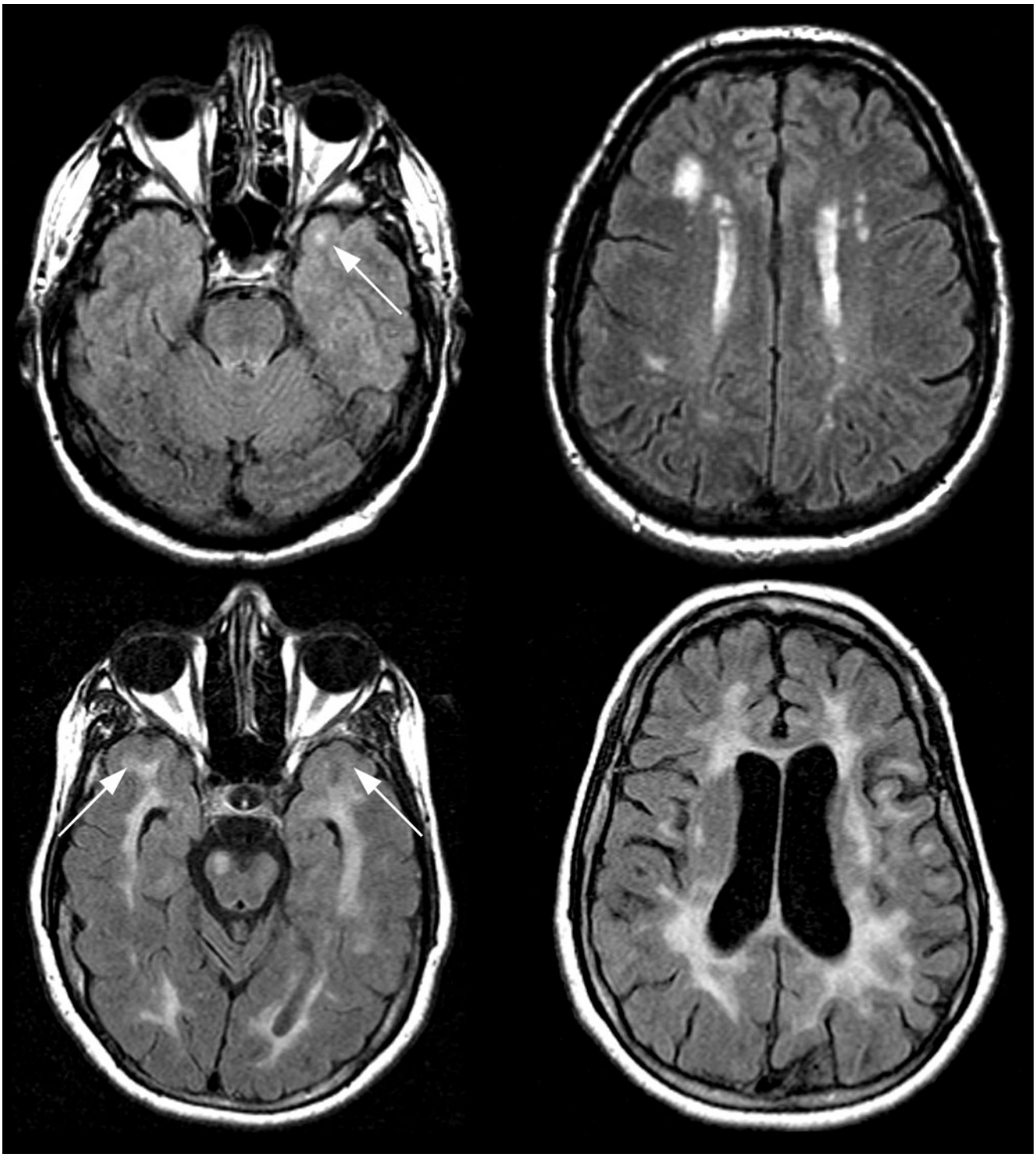

FIGURE 6–11. Magnetic resonance imaging (MRI) in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

The anterior temporal lobe is a notable site of predilection for hyperintensities in CADASIL. The MRI scan from a young patient, who has a *NOTCH3* mutation (top row) but minimal clinical symptoms, shows a few areas of white matter hyperintensity, including a characteristic lesion at the gray-white junction in the anterior temporal lobe (arrow, left). A few hyperintensities are seen in the centrum semiovale. An older symptomatic and demented CADASIL patient (bottom row) has even more extensive and confluent white matter abnormalities in anterior temporal lobes bilaterally (arrows, left). The image on the right shows confluent white matter hyperintensities involving most of the periventricular white matter. Similar hyperintensities occur in other forms of vascular dementia, so at this point, CADASIL usually can be recognized only when an autosomal dominant pattern of a similar illness in other family members is elicited.

medication side effects, and malingering. Normal MRI and FDG-PET scans will help confirm that a patient is willfully unable to perform his daily care and does not have a dementing disease, even though he or she performs very poorly during the clinical examination and neuropsychological testing.

Emerging Neuroimaging Methods

With the rapid development of new technology, neuroimaging will provide important new insights and play an increasing role in dementia care. Many other neuroimaging methods await further research and development.

Advanced Image Analysis

Dramatic increases in computing power and significant advances in image processing algorithms and statistical methods will improve the accuracy of brain scan interpretation. Clinical studies still rely primarily on simple standard planar image displays and subjective interpretation of findings without reference to standardized data for comparison. However, much more can be done. Imaging data can be manipulated to show the brain in any angle of view or in four dimensions (by incorporating serial studies into processing algorithms). As scanner resolution has improved, the need to reduce this information to a more manageable form for interpretation has been compounded.

Advanced image analysis methods are widely used in research and can meet most practical challenges; however, regulatory and practical hurdles must be overcome before these methods are widely adopted in everyday medical practice. Nevertheless, these methods already have shown their clinical utility. Translating and warping images into a uniform stereotactic space permits individual and group comparisons (Herholz et al. 2002; Minoshima et al. 1995). New methods of image processing, such as three-dimensional stereotactic surface projection (3D-SSP) mapping, can reduce the number of images that have to be mentally manipulated for interpretation (see Figures 6–5 and 6–6). Peak pixel values for the lateral and medial brain surfaces are derived by 3D-SSP (Minoshima et al. 1995). The resulting summary images simplify scan displays and can be used to display statistical maps, making interpretation both quicker and more accurate (Burdette et al. 1996). Advanced imaging analysis methods also can improve the ability to recognize abnormalities in AD. The ability of 3D-SSP to display the medial surface of the brain makes it possible to demonstrate that the posterior cingulate gyrus was typically affected early in AD (Minoshima et al. 1994).

Accumulating databases of uniformly acquired images makes it possible to construct normative image atlases for statistical comparison with patient scans. These databases can be tailored to fit the profile of an individual patient. Statistical comparisons can help in deciding which changes recognized by the eye are truly significant and which are due to normal variation. The human brain recognizes asymmetries and contrasting patterns more easily than diffuse or gradual declines in image intensity. Using color scales to display images can be helpful but may also be deceptive. Brain scans provide an overwhelming mass of quantitative information; even a single image is composed of thousands of data points. New statistical methods have been developed to address the problem of simultaneously comparing thousands of nonindependent values. Approaches such as nonparametric permutation testing and false discovery ratio help assure that statistical differences in imaging studies are dependable (Nichols and Hayasaka 2003; Nichols and Holmes 2002).

Neurotransmitter Imaging

Many molecular probes have been developed to examine neurotransmitter function. Cholinergic function is of particular interest in Alzheimer disease. AD damages cholinergic neurons, providing the basis for treatment of AD with cholinesterase inhibitors. With the development of appropriate radioactive ligands, molecular imaging can reveal the manner in which cholinergic deficits develop over time and their relationship to symptoms and patient characteristics. The radioactive-labeled vesamicol analogue IBVM binds to the presynaptic vesicular acetylcholine transporter and can serve as in vivo markers of presynaptic cholinergic terminal density (Kuhl et al. 1996). Molecular imaging using the probe demonstrates that like glucose metabolism, there is a generally uniform distribution of cholinergic terminals throughout the neocortex in cognitively normal individuals. In Alzheimer disease, IBVM binding is decreased.

For technical reasons related to the efficacy of available radiotracers, accurately measuring cholinergic receptors is more challenging. However, significant alterations in muscarinic receptors do not appear to occur in AD (Zubieta et al. 2001). Perhaps most intriguing, observations have been made using a PET radioligand, such as [^{11}C]PMP, that binds to cholinesterase. Although cholinesterase is not a precise indicator of cholinergic neurons, both PET and postmortem studies find similar characteristic decrease of cholinesterase in AD (Kuhl et al. 1999). Peripheral red blood cell assays typically have been

used to assess the potency of cholinesterase inhibitor drugs, even though it is inhibition in the central nervous system that is most relevant. PET studies with [^{11}C]PMP showed that a considerable discrepancy between central and peripheral cholinesterase inhibition could occur after acute treatment with donepezil. Although nearly complete acetylcholinesterase inhibition was expected from red blood cell assays, molecular imaging showed that an average of only 27% inhibition of cholinesterase occurred in the brain, indicating that more effective drugs could be developed (Kuhl et al. 2000).

Although these studies are informative and promising, the potential of cholinergic imaging to improve the diagnosis of dementing diseases or to guide choice of treatment has not yet been explored adequately.

Functional Magnetic Resonance Imaging

Functional MRI (fMRI) utilizes the principle of blood oxygen level–dependent (BOLD) contrast, or blood oxygenation level dependency of MR signals to assess local blood flow in response to a task or during the resting state. It exploits the paramagnetic properties of deoxyhemoglobin that alter the signal on MRI images, and the observation that increased neuronal activity causes a transient increase in blood flow and temporarily decreases deoxyhemoglobin concentration. Under normal conditions, BOLD contrast in the brain reflects microvascular or venous blood.

Several acquisition protocols provide indirect measure of blood flow based on BOLD, including gradient echo epiplanar imaging sequences and spin echo protocols such as EPISTAR (echo-planar imaging and signal targeting with alternating radio frequency) (Edelman et al. 1994; Ogawa et al. 1990). No consensus has yet developed about which of these techniques is preferable. Spin echo techniques appear more selective for capillary blood flow. Fast epiplanar data acquisition is more expensive but less influenced by blood flow and patient movement and may improve temporal resolution and signal-to-noise ratio.

Although fMRI has been used primarily to examine the anatomical correlates of cognitive function in cognitively normal individuals, an increasing number of studies have examined differences in nondemented elderly and those with mild memory impairment and dementia (Bookheimer et al. 2000; Dickerson et al. 2004; Lustig and Buckner 2004). A significant limitation of many fMRI paradigms is that impaired subjects have difficulty performing the cognitive tasks, making it impossible to study patients with more severe dementia. Comparison of subjects is difficult and requires either modification of task difficulty or adjustment for performance. Recent development of an alternative approach using fMRI signals between tasks permits assessment of "default mode activation" (Buckner et al. 2005). Rather than focusing on response to a cognitive stimulus, this strategy examines the coherence of responses between stimuli. This approach avoids problems of variable performance between subjects and within individual subjects during multiple trials and is a promising method for patients with dementia. Broad acceptance of a single cognitive paradigm and multicenter studies showing reliability and diagnostic accuracy are needed before fMRI is ready for clinical use in dementia evaluations.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) applies advanced processing to diffusion-weighted MRI images to provide a measure of white matter integrity. Diffusion of protons in white matter is constrained by the direction of fiber tracts. Through the calculation of vectors of diffusion, the directional tendency of proton diffusion can be calculated and displayed. Tissue that displays random diffusion of protons is called isotropic; tissue with restricted or bounded diffusion of protons is anisotropic. In DTI, the extent that directionality is coherent commonly is measured by calculating fractional anisotropy (FA), which ranges on a scale from 0, indicating random diffusion of protons, to 1, indicating highly constrained and linear diffusion. Areas such as the corpus callosum, with highly coherent white matter tracts favoring unidirectional flow, appear on the images as high signal (high FA). Loss of myelin causes loss of isotropy and loss of signal. Using this method, DTI can measure the local disruption of fiber tracts. Traumatic injury, infarction, and axonal loss from neurodegeneration can all cause axonal disruption, but DTI can distinguish among these possibilities using current techniques. DTI data also can be used in fiber tractography. By using tracking algorithms, DTI graphically displays areas of the brain with the same directionality, making possible the representation of well-known fiber tracts and the location of unexpected disruptions.

The application of DTI to AD has been limited. Available studies have found that white matter tracts connecting limbic structures and white matter that myelinates later in brain development are most susceptible to damage in AD and exhibit lower FA values than in cognitively normal individuals. Both limbic tracts and later myelinating tracts are most susceptible to disruption in AD (Medina et al. 2006). These changes may occur early, as demonstrated by Ringman et al. (2007), who found that abnormalities were detected in carriers of familial AD mutations before dementia developed.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) uses an MRI scanner but provides no structural information. Instead, spectra are derived from targeted volumes of brain by measuring a few cubic centimeters and necessarily including both gray and white matter. Magnetic resonance spectra are generated from naturally occurring, biologically important elements such as ^{1}H, ^{31}P, and others (Sanders 1995). The element selected depends on the radio frequency applied. MRS data are displayed as peaks representing the signal that different compounds produce, distributed along a scale that indicates the shift in resonance frequency from the parent element in units of parts per million. MRS does not provide true chemical concentrations. Instead, results are expressed as the ratio of one peak to another, requiring the assumption that the concentration of the comparator compound is relatively stable.

Spectra of ^{1}H are most often studied. Spectra are derived from targeted volumes of brain, and the heights of peaks are used to measure the relative amounts of *N*-acetylaspartate (NAA, a presumed neuronal marker), phosphocreatine (a metabolic marker), choline and myoinositol (presumed glial markers), and, in some pathological states, lactate. The peak produced by creatine is often used for comparison.

Using different frequencies, MRS spectra of ^{31}P can be produced and used to determine the relative abundance of inorganic phosphorus, adenosine triphosphate (a metabolic marker), phosphocreatine, phosphomonoesters, and phosphodiesters. There also is the potential to measure ^{13}C-labeled compounds such as glucose and acetate and to infer rates of metabolism based on measurement of metabolites in these spectra (Ross et al. 2003).

MRS cannot distinguish signals originating from cells and involved in active metabolism from those originating in extracellular pools. It often is helpful to compare spectra in different brain regions, selecting for comparison areas expected to exhibit the most alteration and others that are relatively free of pathology. Results of MRS in dementia must be considered preliminary. Limited evidence indicates that AD and FTD cause a decrease in the NAA-to-creatine ratio and an increase in the myoinositol-to-creatine ratio, with changes in AD especially evident in parietal and posterior cingulate regions (Kantarci et al. 2004; Zhu et al. 2006). Different cell types have different MRS signatures. Recently, a distinctive peak was identified in neuronal progenitor stem cells, suggesting that MRS may be helpful in tracing changes in the cellular composition of specific brain regions (Manganas et al. 2007).

New Neuroimaging Applications

Monitoring Disease Progression and Drug Development

Neuroimaging could potentially be used to monitor disease progression and response to therapy. Cerebral atrophy and synaptic failure increase as dementia progresses in neurodegenerative disease, and these can be observed with MRI and FDG-PET. Imaging abnormalities also increase in vascular dementia as symptoms worsen. Several barriers, however, limit the clinical usefulness of imaging to monitor disease progression. Precise measures of pathology often are not used in clinical studies. Accurately counting the number of small cerebral infarcts can even be difficult. Over time, test-retest variability of many imaging measures is uncertain. Scanner hardware and software are modified frequently. If relying on visual interpretation, imaging changes need to be large and image acquisition and quality must be uniform to produce convincing evidence of disease progression. These requirements seldom are met in clinical practice. Furthermore, imaging is too expensive to replace cognitive measures for the care of individual patients.

These limitations are not as daunting when considering the use of imaging in clinical drug trials. Drug trials compare patient groups rather than making treatment decisions for individual patients. The economic realities also are different. The cost of developing a new drug is huge, and anything that would speed evaluation could save huge amounts of money. Imaging can assist new drug development at many levels. Drugs can be radiolabeled to study their distribution and pharmacokinetics. Imaging can be used to assess the effects of drugs on neurotransmitter function. The use of imaging to improve the accuracy of diagnosis in clinical trials could be expanded from MRI only to include FDG-PET and amyloid imaging. Imaging could help detect the earliest evidence of disease and identify subjects for earlier treatment. Despite the opportunities, the potential of imaging to speed drug development has not yet been fully realized.

Imaging biomarkers need to be validated as a surrogate measure of disease progression (Mueller et al. 2005). Imaging measures are more objective and likely to exhibit less variability than traditional clinical and neuropsychological outcome measures used in trials of drugs for dementia. MRI already has begun to be incorporated as an outcome measure of treatment response in clinical drug

trials (Grundman et al. 2001). Only a few longitudinal studies of AD have used FDG-PET (Alexander et al. 2002), but others are under way. Clinical drug trials will benefit from using the best imaging measure of disease progression, allowing change to be detected over a period of a few months, rather than the much longer time now required. If this can be done, fewer patients will be needed to evaluate new treatments, more drugs can be tested, and studies will be less costly. This certainly is a worthwhile goal.

Personalized Medicine, Risk, and Prognosis

Dementing diseases affect individual patients in remarkably different ways. One patient with AD may be agitated, whereas another with the same dementia severity may be withdrawn. In personalized medicine, the clinician identifies the exact cause of disease early and selects the best treatment, taking into account the individual patient's unique physiology and response to the illness.

Imaging offers the opportunity to significantly advance the goals of this personalized approach to care. Preliminary studies suggest that FDG-PET and amyloid imaging might detect impending dementia in those at genetic risk and accurately predict dementia in those with memory impairment (Chételat et al. 2003; Drzezga et al. 2003; Reiman et al. 1996; Small et al. 2000). Molecular imaging can be used to identify individual variability in the distribution of pathology and use this information to tailor individualized therapies.

AD can cause focal and asymmetric clinical syndromes (Caselli 2000). Likewise, individuals with AD can have FDG-PET scans that appear remarkably different from each other while remaining recognizable variations on a distinctive pattern of hypometabolism. The cause of this metabolic variability is unknown but may affect prognosis and response to treatment. A significant barrier to understanding these phenomena has been the difficulty in recognizing when metabolic asymmetry is significant. Fortunately, new image analysis methods to tackle this problem are being developed and could mark a significant advance (Fletcher et al. 2007). As professionals learn more about dementing illnesses, it becomes clear that stereotypes are misleading. The full potential of therapeutics will not be realized until they can be tailored to address the variation of illness expression in individual patients.

KEY POINTS

- Neuroimaging should be used to answer specific clinical questions.
- Neuroimaging cannot be used to determine whether dementia is present.
- MRI is the preferred structural imaging method in dementia, unless contraindicated.
- MRI is sensitive in identifying vascular lesions, but clinical relevance must be considered.
- The pattern of cerebral hypometabolism reflects clinical symptoms.
- The pattern of cerebral hypometabolism can help distinguish Alzheimer disease from frontotemporal dementia.
- Amyloid plaques can be imaged with PET but may be asymptomatic; their prognostic implications are not yet clear.
- Emerging methods and new applications for neuroimaging in dementia promise an increasing role in dementia diagnosis and personalized care.

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CHAPTER 7

Cognitive Disorders as Psychobiological Processes

Myron F. Weiner, M.D.

In this chapter, I emphasize the complex interaction between mental and physical processes in cognitive disorders and indicate the need for a comprehensive approach to the cognitive and neuropsychiatric symptoms that evolve in their course. The symptoms of persons with cognitive disorders result from interacting social, psychological, physical, and metabolic factors that are unique to each individual; for this reason, every person with cognitive disorder presents a somewhat different clinical picture. Whether the underlying etiology is progressive or static, cognitive and neuropsychiatric symptoms tend to fluctuate from hour to hour and from day to day, depending on each individual's emotional makeup, interpersonal and physical environment, and changes in general health, as well as the nature, location, and progression rate of the underlying process.

Figure 7–1 shows that to the extent that an imbalance between biological adaptive mechanisms (adaptors) and biological stressors produced by a brain injury can be compensated by social or psychological means, a person with a brain injury may be asymptomatic in his or her social context. For example, simplifying social demands may be adequate to prevent emotional storms that arise from conflicting environmental pressures. As biological adaptors such as memory are compromised, they may be compensated by using alternative psychological strategies (taking notes, using a calculator) or social support (filling in by others for memory).

Figure 7–2 shows that as biological, social, and psychological mechanisms fail or become less available, individuals cross a threshold and become symptomatic. Persons whose environmental and social demands are few, such as sedentary elderly retirees, may appear to have intact cognition until very late in the progression of their brain disease; however, the illness of those who are gainfully employed or dealing with other complex situations will become obvious earlier in its course.

Little relationship is evident between individuals' subjective distress and the severity of their cognitive deficit or neuropsychiatric symptoms. Many persons with depression who have trivial objective cognitive findings complain bitterly about their compromised function, whereas persons with early Pick disease or moderate Alzheimer disease may be totally unaware of their egregious behavior

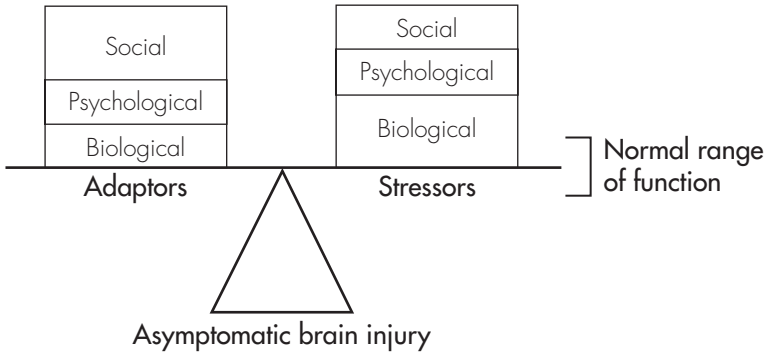

FIGURE 7–1. Asymptomatic brain injury.

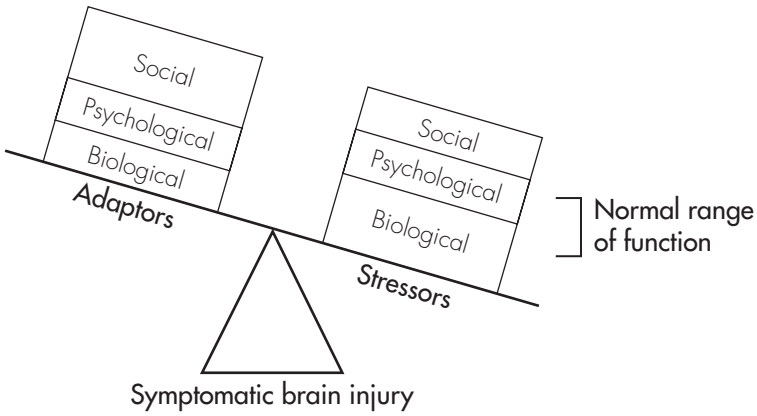

FIGURE 7–2. Symptomatic brain injury.

or cognitive deficits. Although the path from normal cognition to mild cognitive dysfunction to dementia involves crossing thresholds, the passage may be subtle and gradual, as in Alzheimer disease and other primarily cortical dementias, or the threshold for dementia may be crossed abruptly, as in stroke or brain trauma. Significant cognitive impairment may also manifest suddenly after a trivial brain insult, such as a mild concussion. In the latter case, the minor brain insult may reduce the brain's overall integrative capacity to the point that the formerly subthreshold process manifests. In the following example, a trivial head injury sets in motion a chain of unfortunate events.

Case 1

A 69-year-old woman with mild memory deficits had been living and traveling independently and functioning well until she slipped on an ice patch while getting out of her car. She struck her head but did not lose consciousness. She also fractured her hip, was admitted to a hospital, and underwent replacement of her right femoral head. Subsequent to surgery, she developed a persistent delirium. A computed tomographic scan of the brain showed no evidence of intracranial pathology. After a few days, she was transferred to a rehabilitation facility but was unable to relearn how to walk due to her impaired cognition and subsequent inability to cooperate. She was then transferred to a nursing facility, where she had partial clearing of her cognition. Over the succeeding months, it became evident that she was deteriorating cognitively and that her signs and symptoms were those of Alzheimer disease.

An apparent worsening of cognitive or neuropsychiatric symptoms may result from psychological factors in persons whose brain function is already compromised. Intense emotions or emotional states such as anxiety or depression worsen confusion and behavioral symptoms because individuals are unable to deal simultaneously with intense emotion and multiple environmental stimuli. Frequently, the confusion in persons with compromised brain function does not become evident until they experience an emotional crisis or attempt to master a new work or living situation. Another frequent occurrence is the unmasking of cognitive impairment in one spouse by the death of the other. Finally, the onset of a cognitive disorder

may be masked by a clinical presentation suggesting primarily anxiety or depression, as in the following case.

Case 2

An 84-year-old widow was brought by her daughter for a second opinion following the sudden onset of panic attacks accompanied by feelings of depression. She had been treated by her family physician with clonazepam 1 mg two times a day. Although her symptoms were relatively well controlled with this drug, she was unsteady on her feet and oversedated. A change from clonazepam to sertraline 25 mg/day (half tablet) was ineffective, so lorazepam 0.5 mg two times a day was added. This combination controlled her symptoms for several weeks, until she overscheduled herself one day and called that evening in a panic. It became clear in the telephone conversation that she could not keep in mind the physician's recommendation that she increase her dose of sertraline from one-half to one tablet and to continue taking lorazepam 0.5 mg two times a day. She was subsequently diagnosed with Alzheimer disease.

The threshold model of cognitive disorders, shown in Figure 7–2, applies to both cognitive and neuropsychiatric symptoms, including disorders of executive dysfunction, emotion, perception, and ideation. Symptoms of executive dysfunction range from apathy to impulsivity, poor judgment, and verbal or physical aggression. Although executive dysfunction is related in part to memory and other information processing deficits, cognitively impaired persons with relatively mild memory deficits frequently lose their ability to independently initiate complex activities or they become disinhibited. An individual may strike out verbally or physically when frustrated or distressed, or become tearful with minimal provocation.

Case 3

Consultation was requested for a 69-year-old man who had been admitted to a special care unit for disturbed dementia patients. The physician greeted the patient, who was seated at a dining room table, and they had a pleasant interaction concerning the patient's former business and the types of merchandise he had sold. The patient acknowledged that he had difficulty with memory, which was annoying, and also with word finding. The examiner noted that the patient was seated in a wheelchair and asked the patient if he had difficulty walking. The patient said that he had mild difficulty walking due to his Parkinson disease. A few minutes later, the patient began attempting to stand and was told by an attendant to seat himself. This angered the patient. He pulled back from the table and wheeled himself away. When another attendant offered to tie his shoelaces, he began an angry, accusatory outburst, saying that he would decide if his laces needed to be tied and that if they did, he would do it himself. The angry interaction between the patient and the staff members escalated as he again began to stand, and they attempted to reseat him. He finally stood up and was able to walk by pushing the wheelchair. When the consultant again approached the patient, another angry outburst ensued, and the patient said he would never speak to the examiner again. The staff had a particularly difficult time with this man because his memory was far less impaired than that of others on the unit; they had difficulty understanding that his impairment was largely in the realm of judgment and emotional control.

Executive dysfunction is especially a problem when caregivers view impaired persons as psychologically clinging, ill tempered, or vindictive and begin to deal with them as if they were manipulative or deliberately cruel (Williamson et al. 2005).

Personality Function in Cognitive Disorders

Although the mind is not independent of the brain, it is useful to conceptualize the mind as having a dynamic structure of its own that balances and integrates the demands of psychological and physiological forces. The mind mediates between the ego functions of adaptation, coping, and defense; the pressure of conscious wishes and the sexual, aggressive, and other unconscious drives that comprise the Freudian id; and internalized standards of behavior that comprise superego functions. In persons with cognitive impairment, impaired adaptive or coping ability may cause emotional symptoms, perceptual or ideational disturbances, or problem behaviors. The nature of these symptoms and behaviors is partly determined by preexisting personality structure and the changed relationship between individuals, others in their environment, and their former or ideal selves. For some persons, the change may be in the ability to nurture others or to competently maintain a household; for others, it may be the ability to function at a paying job. Thus, in the early stage of a progressive cognitive disorder, loss of ability to function in ways that are significant to the individual may cause greater subjective distress than the person's global loss of function. For example, a man with early Alzheimer disease who prided himself on his organizational ability became enormously distressed when he was unable to gather income tax information for his accountant and literally spent days and nights repeatedly making lists of his assets that he was unable to organize.

Coping Ability

The concept of adaptive or coping ability (ego strength) is important for understanding much of the neuropsychiatric phenomenology of cognitive disorders. To cope adequately with the demands of everyday living, a person must have sufficient ego strength to deal with the external environment while appropriately suppressing, repressing, or sublimating the demands of unconscious drives and conscience, or finding adequate substitutes for meeting those demands. When a person experiences impairment of the ability to suppress, repress, sublimate, or substitute, psychological defense mechanisms come into play (Freud 1946).

Coping ability is related in part to cognitive integrity and to the ability to make positive relationships with others, control impulses, test reality, take psychological or physical action, and assume responsibility for actions taken. Coping ability also depends on the biological integrity of the person as a whole—that is, whether the person has sufficient psychological and physical energy and physical ability to attend to matters outside of maintaining the integrity of his or her physical being. Many factors can impinge on biological integrity. For example, a cognitively intact person in severe physical distress may have little ability to deal effectively with matters other than seeking immediate relief.

Case 4

A 57-year-old physician arrived by ambulance at an emergency facility with severe chest pain due to an impending myocardial infarction. The trip had been complicated by difficulties transporting him from his residence to the ambulance, and by additional difficulty starting an intravenous infusion while in the ambulance, as he was in mild shock and his arm veins had collapsed. When asked after his arrival at the hospital by his physician whether he would prefer treatment with a balloon angioplasty or a fibrinolytic agent, the patient's response was, "I'm in no condition to make that decision. You be the doctor! Now please get me something for my pain!"

By contrast, trivial distractions can make it impossible for cognitively impaired persons to concentrate. Thus, an early complaint of many persons with evolving cognitive disorders, including the cognitive dysfunction of normal aging, is that they can no longer multitask; rather than supplying enrichment and mutual stimulation, each of the multiple tasks becomes a distraction from the others.

Personality Structure

Personality is the sum of an individual's habitual coping/defensive patterns. The 10 types of personality disorder described in DSM-IV-TR are based on frequently occurring maladaptive clusters of coping/defensive patterns (American Psychiatric Association 2000). The patterns are maladaptive because they are highly stereotyped and inflexible. For example, many persons have histrionic traits; they enjoy self-display and being the center of attention, as do persons with a histrionic personality disorder. Although the person with a histrionic trait is still able to function when not the center of attention, the person with a histrionic personality disorder often seeks attention through physical symptoms or outrageous behavior when he or she is unable to secure it through ordinary self-display.

Premorbid personality has much to do with the ability to pay attention, to establish positive relationships with others, to test reality, and to assume responsibility. Cognitive impairment often uncovers aspects of the personality that were partially suppressed or totally repressed when the individual was biologically intact. Individuals who were formerly able to suppress their suspiciousness may become less able to do for themselves than their objective degree of impairment would suggest.

Those who relish their autonomy may strive in unrealistic ways to maintain their autonomy and refuse appropriate help. This is often seen in the case of widowed elders, independent for many years, who refuse the help of neighbors and the public health nurse in meeting their needs as their sight, hearing, cognitive function, and physical health fail.

Through biographical information provided by the patient and others, it is possible to determine which behavior patterns are transient responses and which are largely unalterable aspects of the individual's personality. This information also gives cues for managing patients. The knowledge, for example, that a particular patient has had a lifelong inability to share would indicate that this patient could not comfortably tolerate a nursing home setting that involved sharing a room. Also, a person who has been dominant in relationships throughout life will find it difficult to be under the control of others but may be induced to share control of activities such as writing checks.

Cognitive Disorders as Psychological Processes

A dynamic psychological view makes it easier to understand the fluctuating and changing cognitive and behavioral symptoms of persons with impaired brain function and to provide support for them. Emotionally healthy persons are kept alert and are stimulated by small increments of anxiety. Intense anxiety, on the other hand, impairs con-

centration, learning, and behavioral control. Thus, changes in a cognitively impaired person's level of emotional tension during the course of a day can produce large fluctuations in cognition, coping ability, and behavioral control. The same is true of sensory input. Adequate sensory input helps to maintain orientation in time and space; overwhelming input in the form of too novel or too many stimuli increases confusion and impairs self-control. A cause of consternation for many caregivers is the persistence of perceptual priming by emotional enhancement of memory (LaBar et al. 2005). This phenomenon, possibly mediated by the basolateral amygdala (Paz et al. 2006), enables persons with memory impairment to remember emotionally charged events. For this reason, impaired persons are frequently accused of being more cognitively intact than they appear because they remember emotionally charged events, such as having been told not to drive, but not day-to-day elements of living, such as the location of items in the kitchen.

Persons with cognitive disorders may use any of the coping mechanisms and defense mechanisms outlined in Tables 7–1 and 7–2 at some point during the course of their underlying illness. Table 7–1 indicates positive adaptive or coping mechanisms.

The capacity for positive adaptation involves the ability to assess information from multiple internal and external sources, to make decisions based on that information, and to follow through with an appropriate response or set of responses. Making decisions and taking action involve the assumption of responsibility—that is, acknowledging one's actions as a product of one's own wishes or fears. Psychologically healthy persons tend to seek out novel stimuli and attempt to master and attribute meaning to their environment. They learn when to trust their own judgment and the judgment of others, and they maintain hope that they can positively influence the world about them and derive a sense of satisfaction from their activities.

Other coping mechanisms include sublimation, suppression, altruism, anticipation, and humor (Vaillant 1977). Sublimation is converting physical and psychological drives into socially acceptable thoughts and actions. Suppression is waiting for the best moment to express a thought or to act. Altruism is doing for others without expectation of personal gain. Anticipation involves planning constructive action and differs from worry or rumination, which tend to lead to inaction. Humor is the ability to enjoy surprise and uncertainty and to surprise others in pleasant ways. Many persons with Alzheimer disease are able to continue using these positive coping mechanisms until late in the disease, possibly due to the relative preservation of their frontal circuitry. By contrast, there is rapid erosion of executive function in many persons with frontotemporal dementias.

TABLE 7–1. Coping mechanisms

- Decision making
- Mobilization of will
- Assumption of responsibility
- Stimulus seeking
- Mastery
- Attribution of meaning
- Trust of oneself and important others
- Hope

Coping mechanisms often begin to fail in cognitively impaired persons. Because decision making and follow-through become difficult, many persons with cognitive impairment become angry with family caregivers who attempt to help with decision-making ability and to support their initiative by suggesting activities in which they might participate. Caregivers are often seen as attempting to dominate, interfere, or undermine the autonomy of the cognitively impaired person. Instead of acknowledging an inability to remember, individuals with cognitive impairment blame others when they cannot find lost objects, and may develop transient or relatively fixed delusions that others are stealing. In contrast to the delusions of people with schizophrenia or mood disorders, the delusions of cognitively impaired persons are not (in my experience) supported by secondary elaborations or a complicated delusional system. These individuals do not, for example, explain alleged thefts by insisting that others can read their minds and thereby know where objects are hidden. Persons with impaired executive function often rationalize inappropriate behaviors, as did a man with frontotemporal dementia who thought it entirely appropriate to loudly point out fat women in a shopping mall. Avoidance of new stimuli is common and is often viewed by family members as a depressive symptom. As comprehension and mastery of the environment become more difficult, persons who are aware of their deficits have feelings of hopelessness and helplessness. These individuals, instead of sublimating, may demonstrate their raw drives, sometimes in the form of inappropriate aggression or inappropriate genital display. Lack of ability to suppress leads to impatience. Self-centeredness replaces altruism as impaired awareness of others reduces the capacity for empathy. Anticipation gives way to impulsiveness or inertia. Laughter in reaction to novel stimuli is replaced by startle and upset.

Some individuals cope well with cognitive impairment. They acknowledge their deficits and consciously develop compensatory strategies such as making lists, avoiding unfamiliar places, asking questions, and depending on others

TABLE 7–2. Defense mechanisms

Neurotic	Immature	Psychotic
Repression	Projection	Denial of external reality
Intellectualization	Fantasy	Distortion
Isolation	Hypochondriasis	Delusional projection
Displacement	Passive-aggressive behavior	
Reaction formation	Acting out	
Dissociation		

Source. Adapted from Vaillant 1977.

to solve problems. Often, however, there is damage to the brain regions that enable self-awareness. Persons with Alzheimer disease, for example, are frequently unaware of their memory deficits (Sevush and Leve 1993). For these individuals, impaired attention makes it difficult to productively employ strategies such as list making; they ignore the reminder lists that they place prominently throughout their homes and forget to use the pad they have placed by the telephone to write down messages. Persons with frontal lobe damage are unaware of their impaired judgment. Persons with Wernicke aphasia frequently do not grasp their inability to understand what others are trying to communicate to them and may come to believe that others are deliberately trying to confuse them. Without self-awareness, individuals are less likely to develop conscious compensatory mechanisms. Cognitively impaired persons whose coping mechanisms and self-awareness are intact may experience mourning for the loss of their former self (Bahro et al. 1995).

Many persons with slight cognitive impairment become self-critical and experience lowered self-esteem resulting from an imbalance between their ego ideal, their performance standards, and their impaired coping ability. For example, a person may be unable to live up to an ego ideal that includes productive work. In addition, self-criticisms that would ordinarily be dismissed overwhelm the personality and flood it with guilt and self-recrimination. This type of psychological explanation may account for transient episodes of depression that often occur during early progressive cognitive disorders.

The defense mechanisms listed in Table 7–2 represent failures of positive coping ability. They are mechanisms used to deal with inadequate capacity to perceive, integrate, and act effectively on stimuli that impinge on the organism from within and without. As originally formulated (Freud 1946), these mechanisms referred to defenses against awareness of unconscious wishes or conflict, but they can also defend against awareness of unpleasant or frightening aspects of reality. The defense mechanisms listed in Table 7–2 are classified by Vaillant (1977) into three groups—neurotic, immature, and psychotic—based on the frequency with which they are associated with various mental disorders and stages of development.

The defenses adopted by persons with cognitive impairment depend on their premorbid personality, their environment, and the rate at which their illness progresses. Rapidly progressive brain disorders seem to provoke the more primitive defense mechanisms of denial, distortion, and delusional projection. This is probably the psychological basis for the association between early psychotic symptoms and more rapid progression of Alzheimer disease (Ropacki and Jeste 2005). Denial, which is frequent in all forms of dementing illness, differs from neglect, such as the syndrome of contralateral neglect that often accompanies lesions of the right (nondominant) hemisphere (Denny-Brown et al. 1954). The apparent denial by many cognitively impaired patients of their defects in memory and judgment is often due to losing the neuronal substrate for self-observation. In a study of individuals with Alzheimer disease, Derouesne et al. (1999) showed that persons with mild Alzheimer disease were aware of the existence of their deficits but were not aware of the severity of deficit or the degree of incapacity. Decreased awareness correlated positively with apathy and with frontal perfusion deficits detected with single photon emission computed tomography; however, as would be expected from the psychological standpoint, persons with greater awareness of deficit were more anxious.

Defenses from Vaillant's (1977) category of neurotic mechanisms are not prominent in dementing disorders. Some persons appear to accept their impairment but then demonstrate by their behavior that they do not recognize any impairment. Displacement is occasionally employed, as indicated in the following case.

Case 5

A 67-year-old widow was being evaluated for symptoms of dementia that had progressed over a 4-year period. When asked if she had any difficulties, she replied that she had a painful ankle and showed her leather-braced

ankle to the examiner. She said that since she had started wearing the brace, the arthritis in her ankle was considerably less troublesome. Later, the examiner began a formal inquiry into her cognitive state, asking questions to test her memory, concentration, and fund of information. When at a loss for an answer to a question, she would reply that her ankle was hurting and interfering with her concentration.

Other persons develop reaction formations against their impairment, putting in longer hours at work to compensate for their slowed thinking and impaired comprehension. On one occasion, it was necessary to hospitalize a man with early dementia who had become delirious from working long hours and losing sleep in an effort to keep up with his work.

The catastrophic reactions (Goldstein 1942) that occasionally occur when persons with cognitive impairment are faced with intense emotional stimuli or unmanageable cognitive input may take the form of a transient confusional state. For example, as in the following example, a person might suddenly become unable to recognize a familiar environment or undergo a sudden emotional regression and begin calling for long-dead parents or other relatives as though they were still alive.

Case 6

A 70-year-old man with Alzheimer disease became frightened when he was unable to recognize his wife and began calling out for his mother. He remained in this excited state until he was calmed by his son, whom he was able to recognize.

Catastrophic reactions are usually self-limited and are best contained by distraction or by removing the aggravating environmental stimuli.

Immature defense mechanisms are often employed by persons with cognitive impairment. Projection in the form of blaming (as opposed to delusional projection) often occurs early in the course of dementing illnesses. A wife will exclaim with irritation that her husband did not tell her the children were coming to visit, despite having participated in planning the visit. A cognitively impaired husband will rage at his wife for hiding the car keys that he misplaced.

The use of fantasy as a defense mechanism is impaired because of attention and memory deficits, but somatic preoccupation is often encountered, with a host of physical complaints being offered to distract from the potential awareness of decreased cognitive ability. Rather than reacting with passive opposition (which involves the ability to inhibit an impulse), persons with cognitive impairment often express direct aggression in the form of blaming. Acting out is also common, precisely because these individuals lack the ability to inhibit their behavior. Thus, inappropriate aggression or sexual display may sometimes occur. For example, a nursing home roommate may be screamed at for intruding instead of being politely asked to leave, or open masturbation may occur in response to genital stimulation from tight clothing.

Psychotic defenses occur frequently when cognitive impairment reaches the stage of moderate dementia. The denial of impairment is common, as previously noted. Distortion is illustrated by a person's thinking that he or she is in a prison rather than a nursing home. Delusional projection may occur, for example, when a person who is unaware of having a defective memory attributes an inability to keep track of house keys to others deliberately removing them. Persons who have reached midstage dementia occasionally develop a transient delusional system to support such contentions, as in the following example.

Case 7

A woman with severe cognitive impairment was unable to comprehend her environment. She dealt with the problem by refusing to leave her house to venture into an unfamiliar environment. She responded to all visitors as intruders, calling them whores and attempting to drive them off in an effort to keep her environment simple and comprehensible.

Delusion formation also occurs without the element of projection, especially in persons who develop prosopagnosia, the inability to identify faces. A man with prosopagnosia became very concerned when he failed to recognize his wife while on a trip. He became agitated and exclaimed that he was being kidnapped. Such delusions are usually transient and tend to occur when the environment becomes too demanding.

Regression is another prominent mechanism employed by persons with cognitive impairment. It may manifest as infantile clinging to loved ones, avoidance of strangers, tantrums, inappropriate or unnecessary dependence, and attempts to obtain special attention from others. When regression takes the form of physical clinging to other persons, dolls or stuffed animals can often be substituted for the constant presence of another person. This parallels the use of transitional objects to serve the emotional needs of young children who also lack object constancy—the ability to recognize that an object no longer in reach or in view can continue to exist (Piaget 1954). Whether such cognitive regression occurs with progressive cognitive disorders has not been formally tested, but the "shadowing" behavior of many persons with dementia suggests that it probably does occur. Many caregivers are distressed when dementia patients knock impatiently on the bathroom door demanding entrance while the caregiver is attending to personal needs.

As with young children, reassurances that one will soon reappear are often insufficient. Young children become upset by recalling the unpleasurable experience of loss; cognitively impaired persons become upset in some measure because of an inability to remember the just-given promise to return.

The psychological mechanism of splitting, which is frequently employed by persons with cognitive impairment, may be part of the regressive process. This mechanism, theorized by Klein (1957) to be characteristic of an early stage of personality development, involves the active separation of good from bad experiences, perceptions, and emotions linked to other persons. Thus, as in the following example, the frustrating aspects of an emotionally important person are split off from his or her caring aspects to form two entirely separate persons, one who is all good and another who is all bad.

Case 8

A woman with Alzheimer disease was having increasing difficulty identifying her husband. One night, frustrated with her seemingly endless repetitiveness, her husband spoke harshly to her. The woman reacted with alarm. She perceived him as having become two persons, both of whom were claiming to be her husband. Frightened and unable to determine which one was her real husband, she fled the house to the home of a neighbor and had the neighbor call the police. The following day, she was still not certain which of the two men was her husband. She could not fathom how her real husband could be so unkind to her and had resolved her psychological problem by splitting him in two.

The splitting process described in the preceding case may also contribute to the development of Capgras syndrome, in which the patient believes that persons in his or her environment are not their real selves, but doubles.

Neuropsychiatric Concomitants of Dementing Illnesses

Psychiatric disorders in people with dementia are discussed in Chapter 15 of this volume, "Psychiatric Disorders in People With Dementia." In this section, I explore common neuropsychiatric symptoms from a psychobiological viewpoint. Although considered individually, these symptoms tend to cluster (Tractenberg et al. 2003); they begin in the transition from normal cognition through the stage of mild cognitive impairment to dementia (Geda et al. 2004), but have greater relationship to functional than to cognitive impairment (Tractenberg et al. 2002a). They are listed in Table 7–3.

Apathy and Withdrawal

The term *apathy* is derived from the Greek *a* (without) + *pathos* (feeling or passion) (Thomas 1889). It has been expanded to mean the absence or lack of feeling, emotion, interest, concern, or motivation (Robinson and Starkstein 2000). The motor aspect of apathy is properly termed *abulia*, from the Greek *a* (without) + *boulon* (will) (Thomas 1889). The latter term was reintroduced by Adams and Fisher (Fisher 1984) to describe the slowness and loss of spontaneity in cerebral disease ranging from its mild form, apathy, to the extreme form, akinetic mutism.

Apathy may be a direct result of or a psychological reaction to brain injury. Apathy, as manifested by social withdrawal, may precede the clinical diagnosis of Alzheimer disease by 2 years or more (Jost and Grossberg 1996). An association has been shown in Alzheimer disease between reduced metabolic activity in the anterior cingulate gyrus and apathy (Migneco et al. 2001); more recently, voxel-based morphometry has shown an association between apathy and tissue loss in the right ventromedial superior frontal gyrus in dementia patients (Rosen et al. 2005). Apathy can also be a psychological reaction to an environment perceived as hostile, unrewarding, or incomprehensible. As a result of feeling overwhelmed, patients with cognitive impairment may withdraw into an environment that they can comprehend, declining to participate in activities outside the home that they formerly enjoyed. When physical withdrawal fails, they may withdraw emotionally as well.

Emotional Disinhibition/ Incontinence

Now termed involuntary emotional expression disorder (IEED; Cummings et al. 2006), emotional disinhibition/ incontinence is a phenomenon in which uncontrollable laughing or crying occurs in response to trivial or no internal or external stimuli. Wilson (1924) hypothesized that the symptom complex results from damage to the corticobulbar tracts, but cerebellar modulation of emotional display may be involved (Parvizi et al. 2001). Lasting from seconds to minutes, the laughing or crying is not usually accompanied by mood change, and may or may not be subjectively distressing. IEED is associated with multiple sclerosis, amyotrophic lateral sclerosis, Parkinson disease, stroke, and traumatic brain injury.

TABLE 7–3. Common neuropsychiatric symptoms

- Apathy and withdrawal
- Emotional disinhibition/incontinence
- Executive dysfunction
  - Loss of self-awareness
  - Agitation
- Depression
- Delirium
- Anxiety/fearfulness
- Sleep-wake disturbances
- Psychotic symptoms

Executive Dysfunction

Executive function includes the ability to think abstractly and plan, initiate, sequence, monitor, and stop complex behavior. Although it is not localized to any portion of the brain, executive function appears to be related to the frontal cortex and its basal ganglia–thalamic connections (Royall et al. 2002). In a review of frontal-subcortical neuronal circuits, Tekin and Cummings (2002) suggested more specific localization of function, with dorsolateral frontal impairment causing general executive dysfunction, orbitofrontal changes leading to disinhibition, and anterior cingulate lesions causing apathy.

Loss of Self-Awareness

Impairment of executive function reduces self-awareness and the ability to learn from experience, to understand the impact of one's behavior on others, and to regulate that behavior. Executive dysfunction can manifest as loss of initiative, impulsivity, emotional indifference, or labile mood. Impairment of self-observation manifests in poor personal hygiene and inappropriate interpersonal conduct. Persons with impaired executive function may indulge in inappropriate sexual activity or display; they may develop abnormal eating patterns such as overeating, eating from the plates of others in restaurants or institutions, and eating of nonfood objects. Case 3 in Chapter 3, "Neuropsychiatric Assessment and Diagnosis," illustrates executive dysfunction. Certain behavioral aspects of executive dysfunction have been termed *agitation*.

Agitation

The psychiatric literature on dementia makes frequent reference to agitation (e.g., Spira and Edelstein 2006), which includes behaviors observed in a cohort of both demented and nondemented nursing home residents and is defined as "inappropriate verbal, vocal, or motor activity that is not explained by needs or confusion per se" (Cohen-Mansfield and Billig 1986, p. 712). The term does not apply to persons crying out because they are hungry, because their incontinence pads need changing, or because they are ignored or abused. Instead, the term *agitation* applies to disruptive vocal or physical behaviors whose origins or meanings are not understood. These behaviors include hitting, kicking, pacing, complaining, verbal or physical clinging, abusive verbalizations, and screaming. An estimated 68% of community-dwelling persons with mild Alzheimer disease demonstrate these behaviors (Tractenberg et al. 2002b). Sachs (2006) suggested that addressing agitation as a symptom of psychiatric illness would represent a great opportunity for therapeutic intervention. However, these behaviors are so heterogeneous that they are unlikely to constitute a syndrome, have a common etiology, or respond as a group to specific behavioral, environmental, or pharmacologic interventions.

Depression

Depression is a complex psychobiological disorder that may manifest in mood alone or may also involve alterations in mood-related patterns of thought, such as guilty rumination, motor activity, and vegetative functions. Physiological factors probably play a greater role in persons with brain damage than in cognitively intact persons who experience depression, and thus certain persons with brain damage have a lower threshold for depression. For depression to be purely psychogenic, a person must be capable of self-observation and of concluding that he or she does not measure up in some way to an ego ideal. Therefore, persons with impaired frontal lobe systems who lack self-awareness are often apathetic but do not become depressed. In other situations, however, depressed mood seems almost entirely a product of physiological factors, as occurs in Cushing disease (Kelly et al. 1983). Depression is common following stroke, but the relationship between depression and the size, location, or cognitive impairment of stroke is unclear (Robinson et al. 1983; Schwartz et al. 1993).

Although evidence is contradictory regarding a relationship between depression and the later occurrence of a cognitive disorder (Chen et al. 1999), much evidence indicates that repeated episodes of mood disorder have a deleterious effect on cognition (Paelecke-Habermann et al. 2005). Whether or not there is a physiological link between depression and the subsequent development of a dementia, many individuals are likely to perceive their impairment of function unconsciously or preconsciously and to experience depressed mood in the context of self-criticism or of mourning their loss.

A possible contribution of brain pathology to depression was shown in a study of 95 persons with autopsy-diagnosed Alzheimer disease. Persons with major depression at the time of nursing home admission or earlier in life had significantly greater hippocampal neuritic plaques and neurofibrillary tangles than did persons without history of depression (Rapp et al. 2006). No significant difference was found, however, between plaque and tangle density in entorhinal cortex, amygdala, or medial frontal cortex, areas more likely to be physiologically associated with depressive symptoms.

Depressive episodes also involve the interaction of genetically determined and environmentally induced vulnerabilities with intercurrent psychological and physiological factors. In a study of depression following stroke, for example, 20% of the depressed patients had a prestroke history of depression (Schwartz et al. 1993). Two studies (Pearlson et al. 1990; Strauss and Ogrocki 1996) found that depressed patients with Alzheimer disease and no previous history of depression had significantly more first-degree relatives with depression than did nondepressed patients with Alzheimer disease.

The underlying biology of depression may be catecholamine or neuroendocrine dysregulation or a phylogenetically determined reaction to a situation experienced as an overwhelming threat to survival (Weiner and Lovitt 1979). Any of these physiological reactions, once established, could become partially autonomous and unresponsive to changes in the precipitating psychological factors.

Injury to or death of neurons depletes the capacity of the ego to deal effectively with the demands of id, superego, and external reality. Brain damage also interferes with the ability to live up to one's ego ideal and results in guilt and lowering of self-esteem. Also, repressed id impulses may erupt or irrational superego demands may increase at the same time that the ego is having greater difficulty interpreting environmental stimuli. Given a biological vulnerability to depression, overt depression may manifest when triggered by stressors such as real or symbolic loss (Engel 1962), illness, brain damage, or aging.

Delirium

From a psychological standpoint, delirium is an acute ego decompensation that results from rapidly developing impairment of coping or adaptive abilities, manifesting when the individual becomes acutely unable to understand the environment and experiences overload from internal or external stimuli. Delirium can occur in a person whose nervous system is intact if the systemic illness is severe and has a rapid onset (e.g., pneumonia accompanied by high fever). More often, an antecedent vulnerability of the central nervous system exists, whether due to central nervous system immaturity or damage. Delirium that occurs in response to a trivial insult suggests an underlying impairment of brain function and is often the presenting symptom in dementia with Lewy bodies.

Persons who experience a sudden decrease in cognitive function become unable to adequately repress unconscious material or to interpret environmental stimuli. Fragmented, repressed memories may pour forth, and persons in the environment become confused with important persons from the past. Therefore, it is easy to understand how a person can appear intact when admitted to a hospital in the company of a familiar loved one but can become delirious in the recovery room with no familiar person present, no orienting cues, and his or her sensorium clouded by anesthetic and analgesic medication.

Anxiety/Fearfulness

Free-floating anxiety may be experienced by those persons with early cognitive decline who have no conscious awareness of their deficits. Individuals with preserved self-observation may experience existential fear of losing their mental capacities and becoming unable to understand and deal with their environment, but more commonly they become fearful of day-to-day situations such as interacting with others and dealing with novelty or complexity. If the person is totally overwhelmed by new or complex environmental demands, a catastrophic response or a delirium may occur. As individuals become more compromised cognitively, their conscious experience of fear may no longer be communicated because of impaired language. Instead, motor manifestations of apprehension about some dimly perceived threat may take the place of verbalized fear. Patients may also lose insight into their impaired cognition and become calmer.

Sleep-Wake Disturbances

Sleep-wake disturbances, which are common among persons with advancing cognitive deficits, include hypersomnia, insomnia, sleep-wake cycle reversal, fragmented sleep, and rapid eye movement (REM) sleep behavior disorder. A study of nursing home patients showed highly fragmented sleep, with both demented and nondemented patients averaging only 40 minutes of sleep per hour during the night (Ancoli-Israel et al. 1989). Comparing Alzheimer disease patients with age-matched control subjects, Bliwise et al. (1989) found no difference in the total amount of sleep; however, patients with Alzheimer disease had poorer quality of sleep, as evidenced by lower mean sleep efficiency, lower percentages of stage 3 and stage 4 sleep, and a higher percentage of stage 1 sleep. Moe et al. (1995) found that in

patients with Alzheimer disease, wakefulness during the night and greater rapid eye movement latency were associated with greater cognitive and functional impairment, suggesting that the neural substrates underlying these processes degenerate at comparable rates.

Persons with cognitive impairment who are not active frequently doze during the day because of boredom and are awake and restless at night because they have already obtained their required sleep during their naps. Elders' sleep is often disturbed by pain, the need to urinate, or the need to take medications. Stimulants such as coffee, tea, or bronchodilators may contribute to the problem.

Hypersomnia

Excessive daytime sleepiness may be related to medications used to control agitation or treat nighttime insomnia, or to the use of anticonvulsants and strongly anticholinergic drugs such as antihistamines, antidiarrheals, and drugs to reduce bladder irritability. Metabolic disturbances stemming from chronic lung disease, renal failure, or liver failure also cause somnolence. From the environmental standpoint, the chief cause of daytime sleepiness is a lack of engaging activities. Daytime sleeping is a way to deal with boredom and to evade the challenge of trying to understand the environment or to initiate behavior. Sometimes, caregivers promote daytime sleeping to ease their burden. Unfortunately, this may promote nighttime wakefulness. A sleeping person is easier to manage than a person who is restless and demanding and does not understand how or why certain things must be done, such as urinating or defecating in the toilet.

Insomnia

Caregivers commonly complain that their charges with cognitive impairment are unable to sleep through the night. Family caregivers look forward to and need relief at night; nursing homes and other institutions are staffed lightly at night. Thus, both family and institutional caregivers bear an extra burden when their charges cannot sleep. Sleep is interrupted by anxiety, but the most common psychiatric syndrome leading to sleep loss is depression. Adding to the sleep difficulty is the excessive stimulant intake in the form of caffeine in coffee, tea, or soft drinks or theophylline for bronchopulmonary disease. In addition, when a person has little daytime physical activity, he or she has little physiological demand for rest. In a study by McCurry et al. (2005), a program of sleep hygiene education for caregivers of patients with Alzheimer disease combined with daily walking and increased light exposure through use of a light box reduced the frequency of nighttime awakenings and total time awake at night.

Reversal of the Sleep-Wake Cycle

Daytime napping and nighttime awakening may lead to reversal of the sleep-wake cycle. For elderly persons, getting to sleep and staying asleep are made difficult by painful arthritis and the need to urinate during the night, the latter being aggravated by diuretics to control blood pressure or to ameliorate heart failure. Sleep apnea, with its frequent interruptions of sleep, is also more common in elderly persons. More often than not, sleep difficulty is produced or aggravated by environmental factors, such as scheduling bedtime too early. When examined objectively, many individuals are found to be sleeping 6–8 hours, but their sleep time begins at 8 P.M. and ends at 2–4 A.M., when they attempt to get up and begin the day. In many cases, individuals get sufficient sleep from napping during the day. Martin et al. (2007) found that nonpharmacologic measures may have modest effects on restoring normal diurnal rhythms in nursing home patients.

Rapid Eye Movement Sleep Behavior Disorder

REM sleep behavior disorder involves violent physical activity during dreaming due to failure of the mechanism that normally produces atonia during REM sleep. Persons with REM sleep behavior disorder who talk loudly, strike out, or jump or fall from bed while dreaming may have synucleinopathies such as Parkinson disease and diffuse Lewy body disease (McKeith et al. 2005).

Psychotic Symptoms

Many persons attempt to compensate for a cognitive impairment with increased alertness. In a hyperalert state, one becomes aware of many environmental stimuli that are not readily understood, so that an attempt to cope by hyperalertness often leads to increased confusion. Suspiciousness is a variant of the hyperalert or hypervigilant state in which the individual interprets stimuli as dangerous. A person who has trouble distinguishing what is safe from what is dangerous may at first view everything as dangerous.

An individual with cognitive impairment experiences frustration and aggravation over having trouble understanding much of a world that he or she could formerly grasp. The person concludes that he or she is being deliberately deceived. In this way, the individual can deny defective perception and integration and no longer needs to explain every event individually or to try to understand each confusing stimulus. For example, a man with dementia does not perceive himself as being unable to identify his wife. Instead, he regards the woman who says she is married to him as an impostor. Delusional thinking also

enables action. Perceiving danger as external enables a person to avoid it or to attack it, thus reducing the unpleasant feeling of helplessness that comes from being confused. Anxiety is dealt with in the same way: no longer able to recognize that anxiety results from inner tension, the person with dementia experiences fear and attributes it to the external environment.

Common delusions include believing that others are in the house (phantom boarders), that one is not in one's own home, that one's spouse is an impostor (Capgras syndrome), and that deceased loved ones are still alive. From the biological standpoint, the suggestion has been made, based on [18F]fluorodeoxyglucose positron emission tomography, that delusional thoughts may be associated with areas of the right prefrontal cortex (Sultzer et al. 2003).

Confabulation and Related Phenomena

When individuals with severe memory impairment, such as those with amnestic syndromes, are asked questions, they often supply elaborate, incorrect answers. When questioned about their place of residence, for example, individuals living at home with a spouse may indicate that they live in a hotel and may provide details about the hotel that are often based on earlier experiences in life. Confabulations do not have the emotional force of delusions, nor do confabulators cling to their stories.

Some individuals with cognitive impairment speak as though long-deceased persons were still present without giving evidence that they have experienced hallucinations. Sometimes, these individuals look for children who long ago grew up and moved away. Common questions by these individuals are, "Where has mother gone?" or "Where are the children? It's time for them to go to school."

Delusional Syndromes

A number of delusional syndromes have been reported in persons with cognitive impairment. They include Capgras syndrome (Burns and Philpot 1987) and Cotard syndrome. In the former, a person has the fixed belief that there are doubles of others and may believe that there are doubles of himself or herself. Individuals with Cotard syndrome believe that parts of their bodies are missing, that they do not exist, or that the world about them does not exist. In dealing with Cotard syndrome, the clinician must suspect major depression in addition to a cognitive disorder. Patients with Alzheimer disease often express the notion that an unseen person is living in the house—the so-called phantom boarder syndrome (Rubin et al. 1988). Patients who are unable to recognize themselves in a mirror may develop the delusion that another person is present. One patient became fearful of entering an automobile because he always saw the face of the same person in the window glass on entering a car.

Illusions

Illusions occur commonly in persons with cognitive impairment. For example, a man with dementia might mistake his wife for his mother. The wife resembles his mother in that she is roughly his mother's age when the mother was last alive, and the notion of "mother" is nurturing and comforting.

Hallucinations

Hallucinations, like delusions, can be explained psychologically as a means to organize an otherwise incomprehensible environment (Weiner 1961). They are often determined by personal needs or wishes, as exemplified by the frequent hallucinations of loved ones. Hallucinations with a physiological component, as in partial complex seizures due to irritable foci, often have an olfactory aura of an unpleasant smell such as burning feathers or burning rubber. Complex hallucinatory phenomena are unlikely to be traceable to any specific brain locus. The possibility of a psychotic phenotype in Alzheimer disease has been suggested based on the relationship of psychotic symptoms with more severe cognitive deficits, more rapid progression of illness, and increased risk for psychosis in affected siblings (Sweet et al. 2003), but the explanation that more primitive psychological compensatory mechanisms are associated with more rapid disease progression seems equally likely.

Charles Bonnet Syndrome

Many patients with cognitive impairment experience a type of intermittent visual hallucinatory state or hallucinosis. Some are disturbed; others are not. Often described as the Charles Bonnet syndrome (Gold and Rabins 1989) and often attributed to visual impairment, the state consists of seeing formed, complex, often stereotyped visual hallucinations. Patients often have the sense that their perceptions are not real and can often speak of them as hallucinations. The hallucinations are not accompanied by delusions and are not present in other sensory modalities. One person saw people in his house with *X*s for eyes. They were never the same people from day to day, and none was recognizable as anyone he knew. He was mildly puzzled by the presence of these people, talked to them (they did not reply), and was able to tolerate their presence very well. Another patient saw individuals with peculiarly colored hair. They seemed to appear in groups and did not speak. Some of them had only half-bodies that they propelled with their

hands. It is now clear that the primary cause of the Charles Bonnet syndrome is the presence of neocortical Lewy bodies (Weiner et al. 2003). These occur in the synucleinopathies Parkinson disease and Parkinson disease with dementia (Lippa et al. 2007), both of which are accompanied by visual hallucinations unrelated to their treatment with dopamine agonists (Williams and Lees 2005). Because of the frequency of REM behavior disorder in these persons, Kulisevsky and Roldan (2004) speculated that this phenomenon may be the intrusion of REM sleep into wakefulness. See Chapter 11, "Dementia With Lewy Bodies and Other Synucleinopathies," for more information.

Suicidal Behavior and Suicide

Suicidal behavior of and completed suicide by persons with cognitive impairment may result from depression or from a combination of factors that include depression (Rubio et al. 2001). Such factors may include other physical illness, social isolation, diminishing financial reserves, diminishing quality of life, and concern over burdening others. Depression-related suicidal thoughts usually diminish when the depression is treated successfully. Suicide is not a great danger in cognitively impaired patients who are unaware of their deficits and who deny or do not comprehend their prognosis. On the other hand, persons with progressive dementias who are painfully aware of their cognitive deficits, their growing dependence on others, and the potential outcome of their disease may choose to end their own lives. They may make successful suicide attempts without being significantly depressed (Rohde et al. 1995).

Suicide attempts are uncommon, but not rare, among patients with Alzheimer disease. Of the 215 Alzheimer disease patients admitted to an inpatient psychiatric setting over a period of 10 years, 16 (7.4%) were admitted following a suicide attempt (Barak and Aizenberg 2002). On the other hand, there is a strong association between Huntington disease and suicide. The difference in suicide prevalence in these two groups is probably related to the relative lack of insight among patients with Alzheimer disease versus the high frequency of mood disorder among patients with Huntington disease, who retain some self-awareness. A review of death certificates for 395 Danish subjects with Huntington disease and 282 unaffected siblings showed that suicide accounted for 5.6% of deaths among those with Huntington disease compared with 2.7% in the general Danish population (Sorensen and Fenger 1992). Risk factors were identified in nine persons with Huntington disease. Of these, eight were male, and six were single or divorced. Duration of illness was 1–14 years. The largest risk factor was having no children. Other factors were living alone, other suicides in the family, contact with other Huntington disease patients, and depression (Lipe et al. 1993). The availability of genetic testing for Huntington disease raises the issue of risk for those certain to develop the disease but who are not yet affected (see Chapter 22, "Ethical Issues and Patterns of Practice"). A survey of Huntington disease predictive testing centers worldwide showed that a total of 44 persons (0.97%) in a cohort of 4,527 test participants had catastrophic events: 5 suicides, 21 suicide attempts, and 18 psychiatric hospitalizations (Almqvist et al. 1999). All persons who committed suicide were symptomatic, whereas only half of the persons attempting suicide and 44% of those with psychiatric hospitalization were symptomatic. Increased risk in this series was associated with unemployment and history of psychiatric illness within 5 years of testing.

Conclusion

Because the symptoms of cognitive disorders are the product of a dynamic interaction between biological and psychological forces, fluctuations in cognitive and behavioral or emotional symptoms are the norm. However, when confronted with increased disorientation in a person with cognitive impairment, a clinician must consider whether the increased confusion or neuropsychiatric symptoms result from progression of the underlying brain disease, metabolic factors, the onset of depression, a change in the relationship between the patient and others, or change in the physical environment.

The clinician's intervention will depend on which variable or group of variables predominates. Having made an adequate diagnosis of the disease underlying the presenting symptoms, a clinician performs appropriate examinations, orders appropriate tests, and assays the effects of interpersonal and environmental changes when the clinical course appears out of line with what is known of the general progress of the illness.

In some cases, cognitive function or neuropsychiatric symptoms will improve when cardiac function is improved, when a urinary tract infection is treated, when the patient is better hydrated, when the environment is simplified by maintaining the same routine every day, or when the person is kept in a familiar environment. In other cases, the patient's status will not change or may actually worsen. The clinician will again investigate to determine whether adverse effects result from medications or unexpected reactions to interpersonal or environmental changes. In all cases, the patient's level of functioning is the result of a delicate balance between factors that become increasingly difficult to evaluate when cognitive disorders progress.

KEY POINTS

- Cognitive changes in persons with brain damage may result from psychosocial factors in addition to changes in brain metabolism or structure.
- Neuropsychiatric symptoms may result from psychosocial factors in addition to changes in brain metabolism or structure.
- Addressing either psychosocial or biological factors can have positive effects if a balance is restored between coping factors and stressors (such as reducing irritability by reducing environmental stimulation, by medication, or a combination of the two).

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PART III

Alzheimer Disease and Other Dementias

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CHAPTER 8

Alzheimer Disease

David S. Geldmacher, M.D.

Epidemiology

Alzheimer disease affects more than 5 million people in the United States and is the most common cause of dementia in the country. The economic burden of caring for patients with dementia is reported as more than $100 billion annually in the United States, exceeding the costs of more common illnesses such as diabetes and arthritis. The number of cases is expected to exceed 13 million in the United States by 2050, with much of the growth attributable to the aging of the population (Hebert et al. 2003).

Dementia prevalence increases exponentially with age, approximately doubling every 5 years, beginning at about 1% at age 60 years and peaking at over 30% by age 85 years. Incidence rates also accelerate with increasing age, ranging from 0.6% for persons age 65–69 years, to 2% for those age 75–79 years, to 8.4% for those age 85 or older (Hebert et al. 1995).

Clinically diagnosed Alzheimer disease, alone or in combination with other illnesses, accounts for up to 90% of reported dementia cases. As many as two-thirds of those cases also have concomitant pathologies, especially cerebrovascular lesions and Lewy bodies, that might contribute to the symptomatic expression of the dementia (Lim et al. 1999).

Many risk factors have been reported. The strongest associations are with age, family history, and apolipoprotein E genotype. The ε4 allele of apolipoprotein E is associated with increased risk, with dose-related effects on overall risk and earlier age at onset. Approximately 12 other gene loci are associated with small increases in risk for sporadic Alzheimer disease, but the specific abnormalities and the mechanisms by which they enhance risk remain unknown (Bertram et al. 2007).

Other putative risk factors for sporadic, late-onset Alzheimer disease include depression, cardiovascular disease (including hypertension), diabetes mellitus, elevated low-density lipoprotein cholesterol level, elevated plasma homocysteine level, low educational achievement, lack of intellectual activity, lack of physical activity, lack of social interaction, lack of leisure activities, and excessive response to stress, as manifested in elevated plasma cortisol levels. Mixed data have been reported on the effect of hormone replacement therapy in postmenopausal women. Some epidemiological studies suggest that hormone replacement therapy lowers risk, but evidence from other clinical trials indicates that hormone replacement therapy may also exacerbate risk for cognitive decline and dementia in women (Shumaker et al. 2004).

Clinical History and Course of Illness

The defining features of Alzheimer disease are progressive deficits in memory and other aspects of cognition. Because the deficits result in reduced ability to perform daily activities, most patients with Alzheimer disease will

become totally dependent on others unless they die of other causes first. The deficits result from synaptic dysfunction and neuronal loss that follow a predictable distribution in the brain. Dysfunction in the hippocampus, limbic cortex, and polymodal association cortex results in the characteristic clinical pattern of Alzheimer disease and assists in its clinical differentiation from other dementing illnesses, which have different anatomical patterns of neuronal dysfunction.

Although losses in domains such as memory, praxis, visual processing, and executive dysfunction are addressed separately in this section, it is important to remember that intact human cognition is a seamless and interdependent whole. Parsing cognitive function into specific domains reflects the conveniences of taxonomy and testing rather than physiological reality.

Cognitive Symptoms

The DSM-IV-TR (American Psychiatric Association 2000) criteria for diagnosis of Alzheimer disease require evidence for impairments in memory and in one other cognitive domain, such as language, praxis, visual processing, or executive function (see Table 8–1). Factor analysis of cognitive testing on 663 patients with probable Alzheimer disease revealed that principal cognitive deficits occur in the domains of memory, language, and praxis (Talwalker 1996), but this study did not include careful assessment of executive function. More recent studies have found executive dysfunction in a majority of patients (Stokholm et al. 2006). Other focal cognitive deficits associated with temporoparietal lesions, such as spatial disorientation, acalculia, and left-right disorientation, also develop in many patients. Table 8–2 lists cognitive domains that are impaired in patients with Alzheimer disease.

Memory

Memory dysfunction is usually the first symptom recognized. It is detectable by neuropsychological tests even in preclinical phases of the disease (Jacobs et al. 1995). The typical memory impairment at onset involves difficulties with learning new information but relative preservation of remote factual information.

Alzheimer disease–related memory change is often described as short-term memory loss. Recent memories are impaired because new information cannot be adequately stored for later recall. As a result, affected persons initially have difficulty remembering recent events. The span of the so-called short term increases over time as the interval since the last period of normal memory function becomes longer. Declarative memory—the fact-oriented memory system that allows individuals to store and recall specific information and experiences—is the most impaired memory system in patients with Alzheimer disease. Procedural memory—knowing how to perform a task—is often better preserved, contributing to the superficial appearance of normality in mild Alzheimer disease. Emotionally toned memories are often better maintained as well. For many individuals, subtle deficits in learning occur prior to overt memory symptoms, but familiar settings, old habits, and preserved social skills mask the problem.

The character of memory loss changes over time. In the mild and moderate stages of the illness, recall of material learned before the onset of memory dysfunction often appears to be preserved. Detailed evaluation of patients reveals that subtle deficits in recall of remote occurrences are frequently present, particularly for specifics such as dates and sequences of events (Storandt et al. 1998). In the late stage, memory dysfunction extends to complete failure of recall for previously well-remembered information, such as the names of a patient's own spouse and children.

Orientation

Although orientation is often considered a cognitive domain separate from memory, orientation to time and orientation to place actually represent specific types of memory. Orientation to person, however, is different. A continuous process of updating memory systems with the passage of time and changes in location is required to maintain orientation. Orientation to time is most vulnerable in patients with Alzheimer disease, but patients often dismiss deficiencies in this ability by stating that the day or date is not important to them or that they have not looked at the news. For healthy older adults, frequent reference to external resources is generally not required to maintain time and day orientation. More relative concepts of time can also be distorted, such that persons with Alzheimer disease may be unable to recount the hour of the day or the time passed since a recent holiday. As the illness progresses, orientation to place becomes more disrupted; this may result in becoming lost in familiar settings while driving or walking. Spatial disorientation later becomes apparent on a smaller scale, such as in the home environment. Family members often report this disorientation as confusion or difficulty in locating rooms. Spatial disorientation is often worse under conditions of low light and can be particularly troublesome for families when the patient cannot find the bathroom. Loss of orientation to self is not typical except in profoundly severe Alzheimer disease, but language or response disturbances may prevent more mildly affected individuals from identifying themselves on questioning.

TABLE 8–1. DSM-IV-TR diagnostic criteria for dementia of Alzheimer's type

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

Source. Reprinted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Copyright 2000, American Psychiatric Association. Used with permission.

Language

Language impairments are a prominent part of the clinical picture of Alzheimer disease. These impairments usually begin as word-finding difficulty in spontaneous speech and may later become severe enough to interrupt the flow of speech and mimic dysfluent aphasia. Initially, patients may complain of frequent tip-of-the-tongue experiences in trying to retrieve words. Circumlocution becomes common. Because some healthy adults have verbal idiosyncrasies or mannerisms that have a similar pattern, family members of patients should be asked to confirm that the worrisome verbal expression pattern is a change.

Language usually becomes progressively vague. It frequently lacks specifics, because patients substitute generic words or broad categories in place of more explicit nouns. Pronouns (*he*, *she*, *they*) are often used in place of proper nouns. The individual also uses more automatic phrases and clichés, particularly when pressed for detailed information. Prosody—the normal rhythm, melody, and emotional intonation of speech—is affected in many patients, particularly in more severe stages. Reading skills and verbal comprehension worsen as the disease progresses. In late stages, global aphasia or muteness (aphemia) is common. When present, disrupted communication patterns contribute to strain in caregiving relationships.

Praxis

Nearly all patients will develop apraxia in more severe stages of Alzheimer disease. Ideomotor apraxia—difficulty in translating an idea into the proper spatially directed action—is most common. This apraxia results in reduced ability to manage clothing fasteners or eating utensils. Some patients lose the conceptual basis of tool use; this is closely related to the loss of semantic knowledge underlying the language and memory problems (Chainay et al. 2006). Another common manifestation of apraxia in more advanced disease is the inability to position parts of the body in space. This form of limb-kinetic apraxia can lead to problems in dressing and also contributes to difficulties in positioning the body, such as getting into a car.

Higher Visual Function

Disorders of higher visual processing are common, and patients can present this symptom in a variant of Alzheimer

TABLE 8–2. Domains of cognitive impairment in Alzheimer disease

Memory
Deficits in learning
Semantic knowledge failure
Repetitiveness
Orientation
Distorted time sense
Language
Anomia and word-finding difficulty
Poor speech content
Impaired prosody
Praxis
Ideomotor apraxia
Limb-kinetic apraxia
Visual processing
Poor object or person recognition
Spatial confusion
Impaired directed attention
Executive dysfunction
Poor planning
Poor judgment
Impairment on complex tasks
Disinhibition

type dementia known as *posterior cortical atrophy*. The dysfunction, which is evident at the level of basic visual processing, includes impaired sensitivity to movement and visual contrast, as well as deficits in depth perception. Visual processing difficulties can be grouped in three main categories: impaired recognition, impaired spatial processing, and impaired visual directed attention. These domains are differentially affected in individual patients. Impaired recognition becomes evident as agnosia, or the inability to recognize familiar objects, which differs from anomia, in which the patient recognizes objects but cannot name them. The inability to recognize faces, known as prosopagnosia, may also evolve, typically in more advanced cases. Problems in spatial processing contribute to spatial disorientation, such as becoming lost in an otherwise familiar environment. Deficits in directed attention become evident in impaired visual exploration, which has important implications for functional tasks, such as driving, that require active scanning of the environment. When severe, spatial processing and directed attention deficits lead to a visual disturbance known as Balint syndrome, an inability to integrate bits of the spatial environment into a coherent whole. As a result, patients have difficulty using vision to voluntarily direct their gaze toward items of interest or to accurately guide hand and arm movements.

Executive Function

Executive dysfunction, including problems with judgment, problem solving, planning, and abstract thought, affects a majority of patients beginning early in the course of Alzheimer disease (Stokholm et al. 2006). These behaviors require individuals to select tasks appropriately, sequence their execution, and monitor performance to ensure successful completion. Intact executive function also requires the suppression of inappropriate responses to the environment. Failures in this area of cognition manifest as problems managing more complicated tasks such as family finances or meal preparation. Socially inappropriate behavior, disinhibition, and poor task persistence may also emerge with worsening executive dysfunction. The presence of executive dysfunction predicts the transition from more benign age-related cognitive changes to early dementia. Executive dysfunction may result in both positive symptoms such as abnormally triggered behaviors and negative symptoms characterized by a failure to respond to a normally motivating circumstance.

Noncognitive and Behavioral Symptoms

Although not specifically included in the formal diagnostic criteria for Alzheimer disease, noncognitive or behavioral symptoms are important aspects of the clinical expression of the disease and sometimes patients present with complaints of thsee symptoms (see Table 8–3). As the disease progresses, these problems often account for a larger proportion of the burden of care than does cognitive dysfunction.

Unawareness of Deficits

Another common noncognitive problem in Alzheimer disease is anosognosia, or unawareness of illness, which occurs in more than 50% of patients. It is often domain specific; a patient acknowledges the presence of forgetfulness but denies any functional consequence of the impairment. In most cases, unawareness of deficits appears to represent a self-monitoring deficit of organic origin and should not be solely attributed to psychological denial. Unawareness of illness is a major impediment to early diagnosis and may reduce the effective implementation of management strategies. Anosognosia is also associated with the risk for dangerous behaviors in patients with dementia (Starkstein et al. 2007).

TABLE 8–3. Typical noncognitive and behavioral manifestations of Alzheimer disease

Anosognosia (unawareness of illness)
Apathy
Poor initiation
Poor persistence
Psychosis
Delusions
Paranoia
Misidentification
Hallucinations
Mood disorders
Depression
Anxiety
Agitation
Nonspecific motor behaviors
Wandering
Pacing
Verbal aggression
Physical aggression
Sundowning

Apathy

Although many clinicians think of agitation as the typical behavioral symptom of Alzheimer disease, personality changes involving passivity and apathy are more frequent early in the illness. Apathy, which is separable from depression and represents an organic loss of motivation, occurs in 25%–50% of patients. Apathy includes diminished initiative, reduced emotional expression, and decreased expressions of affection. Social withdrawal, mood changes, or depression have been found in more than 70% of Alzheimer disease cases, with a mean duration of 2 years prior to diagnosis (Jost and Grossberg 1996).

Psychosis

In contrast to unawareness and apathy, psychosis and agitation tend to occur later in the disease (see Chapter 15, "Psychiatric Disorders in People With Dementia"). Their emergence is associated with more rapid global decline. Estimates of the prevalence of psychotic features in Alzheimer disease vary widely and are prone to selection bias. Population-based estimates suggest that the prevalence for delusions is about 20%; the prevalence of hallucinations is about 15% (Bassiony and Lyketsos 2003). Delusions are often paranoid in character and may lead to accusations of theft, infidelity, and persecution. The delusion that caregivers or family members are impostors or that one's home is not one's real home is a common trigger for wandering or aggression. Hallucinations in Alzheimer disease are more common in the visual domain but sometimes have auditory components. Frequent hallucinations are of deceased parents or siblings, unknown intruders, and animals.

Mood Disorders

Estimates of depression prevalence in dementia vary widely and appear to increase with disease severity. Major depression was observed in about 20% of a sample of patients with Alzheimer disease who had a mean Mini-Mental State Examination (MMSE) score of 18 (Zubenko et al. 2003). Patients with depression prior to the onset of cognitive decline are more likely to experience major depression during the course of their disease. Anxiety can also be expected in about 25% of patients by the time they reach moderate levels of cognitive impairment (Porter 2003). Anxiety tends to be more prominent in the later phases of the illness, but some individuals with Alzheimer disease experience prominent anxious symptoms early in the disease's course. Catastrophic reactions, or intense emotional outbursts of short duration, are associated with anxiety and are characterized by the abrupt onset of tearfulness, aggressive verbalizations or actions, and contrary behaviors. They are often reactions to environmental stressors, thwarted desires, or attempts at personal care. (See also Chapter 15 of this volume.)

Agitation

Agitation is reported in 50%–60% of patients with Alzheimer disease. Agitation is not a specific symptom; it can be divided into several behavior classes, including physical aggression/assaultiveness, verbal aggression and outbursts, and nonaggressive physical behaviors (Cohen-Mansfield and Deutsch 1996). Aggressive behaviors are most clearly linked to delusions and delusional misidentification. Verbal aggression is more common than physical assault. Men and patients with more advanced functional decline are more likely to demonstrate physical or verbal aggression. Aggressive behaviors usually follow an escalating pattern, with verbal outbursts preceding the physical acts. Many episodes of aggression are triggered by attempted caregiver assistance with personal care, especially bathing.

Typical nonaggressive physical behaviors include wandering, pacing, and recurrent purposeless activities. Wandering is sometimes associated with delusional misidentification; the wanderer may be trying to locate his or her

"real" home or locate a "missing" loved one. Wandering has also been associated with poor visuospatial abilities, perhaps reflecting difficulty with incorporating visual information into a coherent spatial map. Dim lighting conditions and nighttime are exacerbating factors for wandering. Risks resulting from wandering include getting lost outdoors and an increased likelihood of fractures. Pacing is somewhat more idiosyncratic, with fewer clearly associated neuropsychological features. Constant pacing contributes to accelerated weight loss in some patients, which can be refractory to dietary interventions unless the locomotor activity is reduced. A more benign form of physical nonaggressive behavior is rummaging in drawers or closets. Rummagers appear to be searching for some item but are often unable to describe what it is. This frequent sorting of personal effects is also associated with delusions of theft.

Sundowning

The term *sundowning* is commonly used to describe predictable increases in confusion and agitated behaviors that occur in the afternoon and evening hours. It is reported in up to 25% of patients, especially those in more advanced disease stages (Little et al. 1995). It is not a unitary symptom and often reflects diurnal variation in other symptoms rather than a specific pathophysiology.

Course of Illness

Most patients pass through a recognizable phase of mild cognitive impairment (MCI) prior to diagnosis. In mild cognitive impairment, deficits in cognition may be identifiable, particularly in the memory domain, but the impairments do not cause disability in usual social or occupational functions.

The average survival time for patients with Alzheimer disease is 4–6 years following diagnosis (Larson et al. 2004). Many individuals have prominent symptoms for several years prior to diagnosis. Approximately half of patients die of complications from global neurological dysfunction, such as immobility and malnutrition; the other half die of other age-related diseases, such as stroke and cancer. Life expectancy is reduced by about 50% (Larson et al. 2004).

Alzheimer disease typically follows a relentlessly progressive course, although there may be periods of relative symptom stability. Symptoms tend to progress less rapidly in both early and late disease, with more rapid losses—especially in activities of daily living—in intermediate stages of the disease.

Alzheimer disease is commonly considered as a series of "stages" to facilitate communication between providers; formal staging instruments are rarely used in clinical settings. Because the pathological expression of the illness follows a generally linear pattern, these stages do not have clear biological correlates. Findings typical for the different stages—mild, moderate, and severe—are depicted in Table 8–4.

Mental Status Findings

The symptom pattern and distribution of pathology in Alzheimer disease dictate that cognition should be the major focus of the mental state examination when dementia is suspected. A well-conducted mental state examination should provide enough information to make a diagnosis by standard criteria (see Appendix C). Differentiating other dementia types may require more extensive cognitive evaluation. The MMSE (Folstein et al. 1975) has become the standard for assessing cognition in practice settings, particularly for the determination of dementia severity. Published age- and education-adjusted norms for the MMSE should be used as the reference for acceptable performance instead of historical or arbitrary cutoffs (Crum et al. 1993). In addition, because the MMSE does not represent a comprehensive assessment of the cognitive impairments associated with Alzheimer disease, it should not be substituted for a thorough cognitive evaluation focusing on the domains most commonly affected.

Global Assessments

Mental status evaluation of patients with cognitive complaints potentially attributable to Alzheimer disease requires assessment of global processes like level of consciousness and thought content to determine whether they meet diagnostic criteria. By definition, dementia can be diagnosed only in the presence of a clear sensorium. Clouding of consciousness suggests a superimposed medical illness with delirium. Thought content is often impoverished, but its organization is linear and logical. Tangential thinking may be suspected, but this should be carefully evaluated to exclude circumlocution related to word-finding difficulties. Loosening of associations is not typical. Psychosis occurs in a minority of individuals, usually in the setting of moderate or more advanced stages of the disease. Delusions with a paranoid character, particularly regarding theft of personal items, are most common. In many cases, these misperceptions are propagated by cognitive deficits. A typical pattern involves a patient forgetting where he or she has placed an item and becoming suspicious that it was stolen; this is often followed by pro-

TABLE 8–4. Typical clinical features of Alzheimer disease, classified by dementia severity

Mild
Impaired memory, may not be obvious to casual observer
Losses in more complicated activities (e.g., meal planning, finances)
Self-care preserved
Passive personality change
Subtle social withdrawal
Little or no active behavioral manifestations
Moderate
Obvious memory impairment
Overt impairment in usual activities (e.g., using stove or telephone)
Self-care failing (e.g., bathing, grooming)
Behavioral difficulties (e.g., sundowning, paranoia)
Variable social skills
Needs supervision
Severe
Memory in fragments only
Possible difficulty recognizing familiar people
Loss of all complex activities
Needs of assistance with self-care
Reduced mobility

gressively more elaborate hiding of personal effects in obscure locations, which are then also forgotten. Hallucinations are much less frequently noted during examination, and occur most often in the context of low illumination and in severe dementia. Judgment declines with dementia severity. Insight into impairments, especially losses in functional skills, is reduced in more than half of patients with Alzheimer disease. Up to 50% of patients will have mood complaints consistent with major or minor depression (Lyketsos et al. 1997); euphoria and hypomania are rare. Affect is usually appropriate to the circumstances but may be blunt and superficial. Anxiety may be provoked by the unfamiliarity of the testing process and environment.

Cognitive Assessments

Learning and Memory

To assess learning and memory, the examiner should ask the patient to repeat and remember three unrelated words. Words that are semantically related, such as *red*, *blue*, and *green*, or *butter*, *eggs*, and *coffee*, are less useful because the patient's memory can be aided by remembering their theme. The words can be repeated as often as desired to ensure that the patient can recall all three words. After a meaningful delay, generally 5 minutes or more of other mental state testing, the patient should be asked to recall the three words. Normal performance is to learn and recall all three words with the first exposure. For those words that the patient cannot remember, further steps may be taken to clarify the nature of the memory impairment. The patient can be given a semantic clue, such as, "One of the words was a kind of flower." Patients with Alzheimer disease are often not helped by semantic cues, whereas individuals with other memory problems, such as those associated with healthy aging, are more likely to benefit from cuing. Recognition memory can be assessed by asking the patient to select the word to be recalled from a list of semantically related words.

Remote memory can be checked by asking the patient to name the last five presidents. Alternatively, if a knowledgeable informant is available to confirm the information, patients might be asked to provide the date when they were married or widowed or the number of grandchildren they have, or to provide details of their military service or employment history.

As an assessment of nonverbal aspects of memory, the patient can be asked to observe while the clinician identifies and hides an object in the examination room. The examiner might show a watch or stethoscope to the patient and place it in a drawer. After a few minutes of ongoing physical or cognitive examination, the patient can be asked to recall what was hidden (object memory) and where (spatial memory).

Because details are lost from remote memory, the patient can be asked to provide details of important historical events, such as the attacks on September 11, 2001, or to recall his or her own experience on learning about the 1963 John F. Kennedy assassination. It is impossible to know how accurate the patient's recall is, but adults with intact memories are usually able to give lucid and richly detailed recollections of how they received the news, how they reacted, whom they were with, and so on. Those with poor memories will often be very vague or give temporally inappropriate replies (e.g., saying they heard about the Pearl Harbor attack at work or on television).

Orientation

Orientation to time, especially dates, is lost early in the course of Alzheimer disease. Many patients with dementia try to minimize aspects of disorientation. Excuses such as a reduced need to keep up with dates are common and can be a cue to the examiner that significant disorienta-

tion may be present. The MMSE provides extensive orientation testing. Additional inquiries about the approximate time of day, the meal that is expected next, or the name of the last major holiday can augment the MMSE. Disorientation to self occurs only in advanced dementia. Its presence in the context of mild or moderate cognitive disability suggests delirium or a primary psychiatric disturbance.

Language

Assessments of language include consideration of naming, comprehension, fluency and effortfulness of speech, sentence repetition, reading, and writing. Language deficits are important in the evaluation of dementia because most healthy older adults have normal spontaneous language except momentary lapses in word finding, especially for proper names.

Impaired naming on examination often correlates with word-finding difficulty in the spontaneous speech of a patient with Alzheimer disease. Naming can be tested with everyday objects available to the examiner, such as a jacket, shoe, or watch. Parts of objects are more difficult to name than whole objects. Therefore, in addition to naming the jacket as a whole, the patient might be asked to name the collar, lapel, sleeve, pocket, and cuff. Responses should be considered correct only if the patient provides a reasonable name for the item. Descriptions of appearance or function should be considered incorrect. Socioeconomic and cultural factors may influence naming of some items, but most individuals should name most of the items effortlessly.

Persons with Alzheimer disease typically have fluent speech that may seem empty, with reduced meaningful content. Except in advanced stages, the patient's comprehension is usually sufficient to understand basic conversation and follow simple examination-related commands. Comprehension for syntactically complex instructions is more vulnerable. It can be tested with a two-step command in which the word order does not reflect the order of the intended action (e.g., "Before pointing to the door, point to the ceiling"). This is somewhat more language intensive and less memory dependent than the three-step, syntactically straightforward command on the MMSE.

Praxis and Temporoparietal Function

A brief sequence of commands can simultaneously assess language comprehension, ideomotor praxis, and left-right orientation. The patient should be asked to carry out a different imagined action with each hand (e.g., using a hammer to hit a nail, turning a key to open a lock). A subsequent two-handed task, such as slicing bread, tests the patient's ability to integrate the actions of both hemispheres in a single, spatially specific task. These can be followed with commands that require the patient to correctly identify right and left, in reference to his or her own body (e.g., "Touch your right hand to your left ear") and to the examiner's body (e.g., "Point to my left hand with your left hand"). Most cognitively normal adults will perform these tasks effortlessly. Patients with mild dementia most often perform poorly on the two-handed praxis test.

Visual and Spatial Processing

Many persons with Alzheimer disease have problems in processing perspective and apparent depth. This processing can be tested by having the patient copy a drawing of a cube or other simple three-dimensional figure. Normal performance is to accurately depict three sides and three dimensions. Even patients with mild dementia may represent three visible surfaces, with no attempt to show their three-dimensional relationship (see Figure 8–1).

The integration of motor behavior in space can be further tested with the clock-drawing test, which assesses multiple realms of cognition, including executive function (planning), spatial relationships, and semantic knowledge. Normal performance involves placing all numbers and the hands in the correct position (see Figure 8–2).

Executive Function

Word list fluency can provide useful information about executive function. This common neuropsychological test can be abbreviated for use in a medical assessment. The examiner asks the patient to produce as many words as possible that fit a semantic category, such as animals or fruits. Patients who name fewer than 15 animal names in 1 minute have a high likelihood of dementia (Duff Canning et al. 2004).

Abstract Thought

Abstract reasoning can be assessed by asking the patient to identify abstract similarities in word pairs, such as, "How is a chair like a table?" or "How is an apple like a banana?" Persons with dementia are apt to note the difference rather than a similarity. Alternatively, they are likely to identify a concrete rather than abstract similarity. Examples of concrete responses would include that a chair and table "go together" or that the apple and banana "have skin." Interpretation of proverbs is a useful but less desirable test because of cultural, educational, and generational biases.

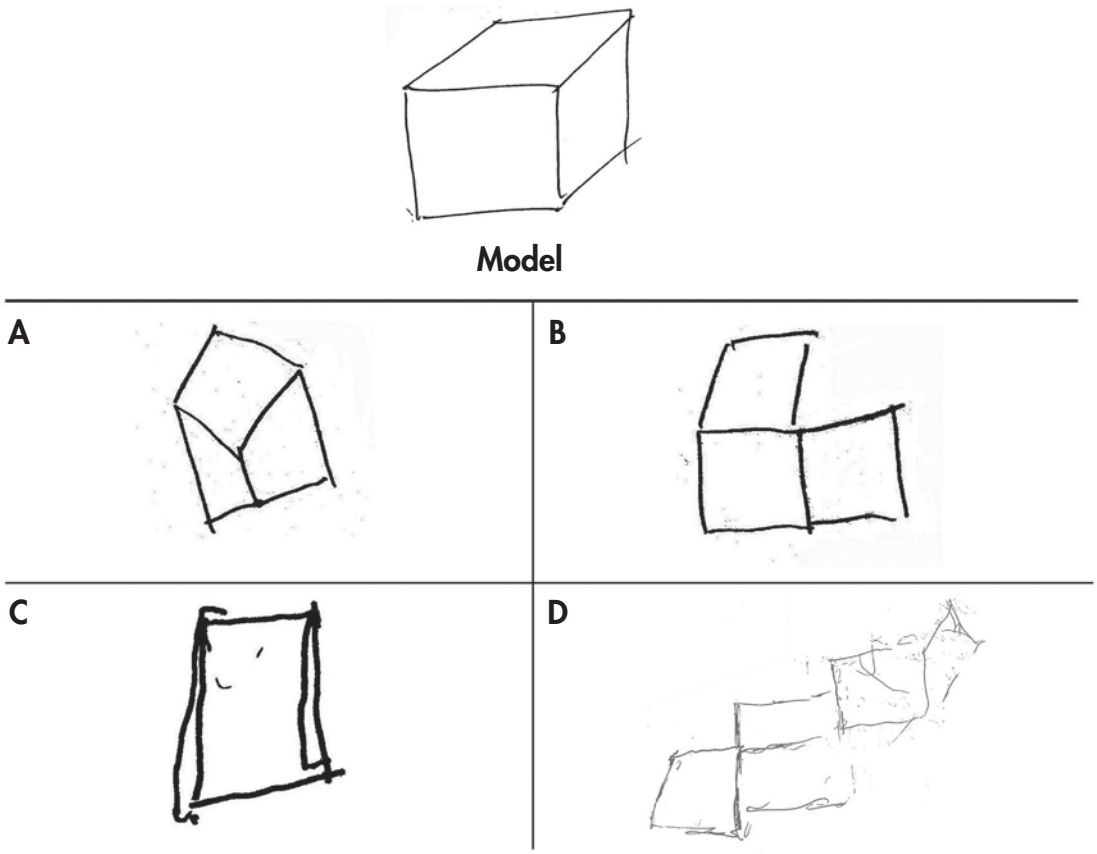

FIGURE 8–1. Examples of abnormal cube copying in patients with Alzheimer disease.
The model figure is the "solid" cube. The other figures show A) loss of three-dimensional aspects, with preserved representation of the three visible sides (Mini-Mental State Examination [MMSE]=22); B) reduced representation of perspective (MMSE=20); C) lost representation of perspective/depth (MMSE=14); and D) perseverative response (MMSE=12); note the fine lines of the drawing are indicative of the patient's uncertainty.

Attention, Concentration, and Working Memory

As a test of attention, concentration, and working memory, which are related parts of cognition, the patient can be asked to add coins, specifically a penny, a dime, a nickel, and a quarter. For this task, it is important that the examiner use the names of the coins, because the working memory system is engaged throughout the subtly complicated process of translating the names to numerical values, performing stepwise addition, and reporting the answer in a unit different from what was provided. Individuals without dementia are not overly threatened by this task because it involves familiar items and the everyday activity of adding pocket change. It is also sufficiently familiar that a pencil and paper are not required for normal performance. If a person asks for writing tools or dismisses the task as something he or she would need to write down, the clinician should suspect impairment. This pocket change addition task is useful as a cognitive screening tool because it assesses calculation simultaneously with working memory. The patient who answers "36 cents," for example, can add numbers but has failed to include all four coins.

Other tests of working memory or related aspects of attention can be used if pocket change addition is inappropriate, such as when a person is unfamiliar with the common names of U.S. coins. Alternatives include asking the patient to state the months of the year or the days of the week in reverse order. These tasks, however, do not incorporate the complexities of translation and addition of four coins.

Digit span is a common test of primary memory that also depends on attention. The patient is asked to repeat a string of random digits in the order that he or she heard them. Normal performance is to repeat strings of five or more digits correctly. Deficits may be more pronounced when patients are asked to repeat digits in reverse order. Normal performance in the reverse task is to reach a span at least two digits less than in the forward span.

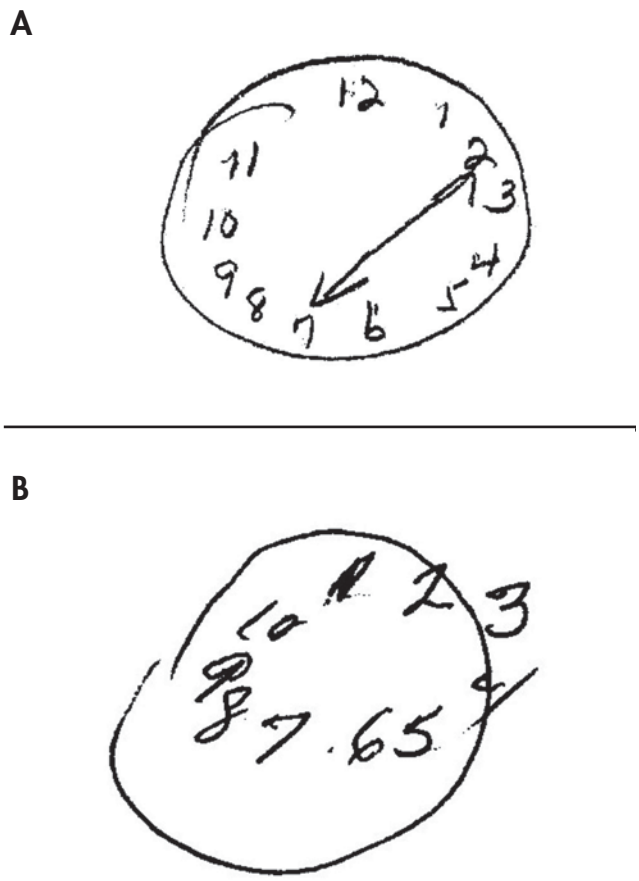

FIGURE 8–2. Freehand responses to the request, "Draw the face of a clock."
The drawings show A) intact spatial organization but reduced semantic knowledge of hand configuration and placement for 2:35 (Mini-Mental State Examination [MMSE]=24) and B) marked spatial disorganization (MMSE=14).

Physical and Neurological Findings

Patients' general physical and neurological examinations remain normal through most of the course of Alzheimer disease. In later stages, extrapyramidal signs (e.g., rigidity) and gait disturbances may become prominent. The point prevalence of myoclonus in Alzheimer disease cohorts is about 5%; it typically worsens in frequency and intensity with increasing disease severity. Multifocal myoclonus may be difficult to distinguish from seizures in later stage patients. Epileptic seizures can be expected to arise in 10%–20% of patients with Alzheimer disease, typically in later stage disease (Mendez et al. 1994).

Laboratory and Imaging Findings

No specific laboratory or imaging test definitively identifies Alzheimer disease. The American Academy of Neurology's evidence-based practice parameter for the diagnosis of dementia (Knopman et al. 2001) recommends blood tests to exclude systemic illnesses as the cause of dementia (see Table 8–5). These tests assess general metabolic and hematological states, as well as thyroid function and vitamin B_{12} levels. Syphilis serology tests are no longer considered part of the routine screening. Apolipoprotein E genotyping has been suggested to reduce the rate of false-positive diagnoses when used with clinical criteria (Mayeux et al. 1998), but this testing is not reimbursed by most insurers and its added value in clinical settings is questionable.

Imaging is recommended as a part of the routine assessment of patients with dementia symptoms. Computed tomography (CT) or magnetic resonance imaging (MRI) is useful to exclude structural lesions that may contribute to the dementia; these include cerebral infarctions, neoplasm, extracerebral fluid collections, and hydrocephalus. Current evidence suggests that the presence of mesial temporal atrophy on MRI strongly supports the likelihood of Alzheimer disease when appropriate clinical features are present (see Figure 8–3) (Wahlund et al. 2005). Positron-emission tomography (PET) scans reveal temporoparietal hypometabolism in patients with Alzheimer disease (Hoffman et al. 2000). In the United States, Medicare has approved PET scanning for the specific indication of distinguishing Alzheimer disease from frontotemporal degeneration.

Cerebrospinal fluid (CSF) examination is not a routine part of the dementia evaluation. Standard CSF tests have a low likelihood of influencing diagnosis in most people with dementia. CSF examination is more useful in cases with serologic evidence of past syphilis, as well as in patients with immunosuppression or atypical dementia symptom patterns, such as young age at onset or very rapid progression. CSF assays for soluble amyloid beta and tau are commercially available. Some clinicians find them useful in cases of difficult differential diagnosis between Alzheimer and non-Alzheimer causes of dementia, but their utility in more routine clinical populations is unclear.

Electroencephalography is also not recommended as part of the routine evaluation of dementia (Knopman et al. 2001). Electroencephalographic findings are nonspecific. They are frequently normal in early stages and evolve toward generalized slowing.

The definitive diagnosis of Alzheimer disease can be made only through autopsy (or biopsy) by identifying appropriate numbers of neuritic plaques and neurofibrillary tangles in specified regions of the brain. The pathological diagnosis requires the presence of a clinical history consistent with dementia, because some individuals with

TABLE 8–5. Recommended testing for the patient presenting with possible dementia screen for depression

Blood tests
Comprehensive chemistry panel, including hepatic and renal function
Complete blood count
Thyroid function tests
Vitamin B_{12} level
Cerebral imaging
Computed tomography (generally sufficient for screening)

Source. Adapted from Knopman et al. 2001.

heavy Alzheimer disease pathological burden retain normal cognitive function (Snowden 2003). Biopsy is not generally recommended for diagnosis; the current state of dementia therapeutics argues that biopsy results are not likely to alter treatment plans. Because of variability in the distribution of plaques and tangles across individuals, a negative biopsy does not exclude Alzheimer disease, although a positive biopsy can confirm it. Despite the absence of a reliable laboratory test to definitively identify Alzheimer disease, clinical diagnosis yields an accuracy of >90% with good concurrence between community-based providers and experts (Mok et al. 2004).

Pathology

On gross examination at autopsy, the brain is usually atrophic with enlarged ventricles and sulci (see Figure 8–4). Total brain weight is invariably reduced, but there is significant overlap with the range of brain weights for cognitively normal older adults. The hallmark pathological features of the disease remain the neuritic plaques and neurofibrillary tangles first described by Alzheimer (1907/1967).

Neuritic Plaques

Neuritic plaques are extracellular and consist primarily of amyloid, an abnormal proteinaceous material, and cellular elements. The form of amyloid deposited in the brains of patients with Alzheimer disease is known as amyloid beta (Aβ). Aβ is a peptide consisting of 39–43 amino acid fragments proteolytically derived from a transmembrane protein known as amyloid precursor protein (APP).

Plaques are microscopic, ranging in diameter from 15μ to 100μ, and are distributed in cortex and limbic nuclei (see Figure 8–5). The highest concentration is found in the hippocampus. Plaques with a high proportion of distorted presynaptic neuronal elements—dystrophic neurites—are known as neuritic plaques. Neurites include intracellular elements of paired helical filaments, lysosomes, and mitochondria. Activated microglial cells are typically found in and around a dense core of extracellular amyloid, whereas fibrillary astrocytes may be seen at the periphery (Wisniewski and Wegiel 1991). Other plaques that lack the dense core of amyloid peptide are known as diffuse plaques. These do not possess significant numbers of dystrophic neurites and are not clearly associated with neuronal loss and cognitive dysfunction. Amyloid can also accumulate in cerebral blood vessels, a condition known as cerebral amyloid angiopathy; this leads to an increased risk for intracerebral lobar hemorrhage.

Neurofibrillary Tangles

Neurofibrillary tangles (NFTs) are the second classical finding in Alzheimer disease (see Figure 8–6). NFTs are intracellular collections of abnormal filaments, which have a distinctive paired helical structure. Although other degenerative illnesses, such as progressive supranuclear palsy, also have NFT pathology, the paired helical structure is unique to Alzheimer disease. NFTs are found throughout the neocortex and limbic nuclei, and their density correlates with the degree of neuronal loss. They are also strongly represented in the basal forebrain, substantia nigra, raphe nuclei, and locus ceruleus. NFTs occupy large areas within the cell bodies of affected pyramidal neurons. This class of neurons is responsible for long axonal projections that facilitate inter- and intrahemispheric communication and appears especially sensitive to the effects of Alzheimer disease (Mann et al. 1985).

Neuropil threads are another neuropathological finding in Alzheimer disease related to NFTs. Neuropil threads are found scattered in the cerebral cortical extracellular matrix. Like NFTs, they consist of paired helical filamentous structures and are also found clustered among the dystrophic neurites of senile plaques.

Synaptic Loss

In Alzheimer disease, widespread cortical synaptic loss occurs and is the major determinant of cognitive disability. Oligomers of Aβ are implicated as direct synaptotoxins (Lacor et al. 2004). The deep layers of the temporal cortex and the hippocampus sustain the greatest degree of synaptic loss. In addition, synaptic inputs to the cortex are re-

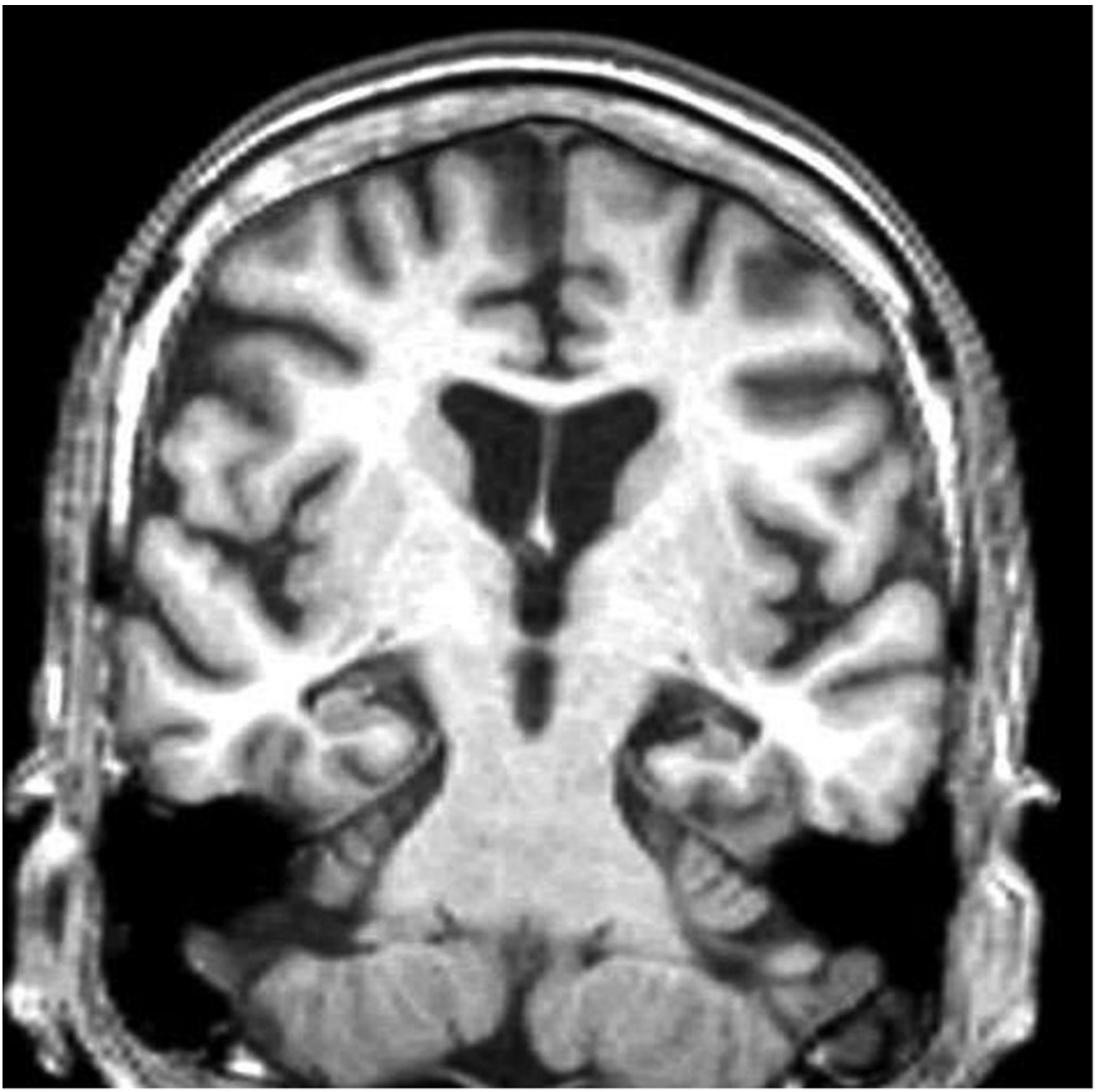

FIGURE 8–3. Coronal T_1-sequence magnetic resonance image through the hippocampal region in a patient with mild Alzheimer disease (MMSE=20).
Ambient cistern is widened between hippocampus and brain stem without concomitant dilatation of the temporal horn of the lateral ventricle. MMSE=Mini-Mental State Examination.

duced up to 40% by the time of the patient's death. The amount of synaptic loss in the frontal cortex correlates well with cognitive impairment in Alzheimer disease (DeKosky and Scheff 1990). Substantial neuronal dropout also occurs in the basal forebrain nuclei, such as the nucleus basalis of Meynert, which produce the neurotransmitter acetylcholine. The number of NFTs in these deep forebrain cholinergic nuclei closely relates to the degree of cognitive dysfunction in Alzheimer disease (Masliah and Terry 1993). A large proportion of synapses and neurons is also lost in the locus ceruleus and the raphe nuclei. Neurons in these brain stem nuclei produce monoamine neurotransmitters and distribute them in the cerebral cortex via long ascending axons. Losses of acetylcholine, serotonin, and norepinephrine inputs to cerebral cortex contribute to the expression of cognitive and behavioral symptoms.

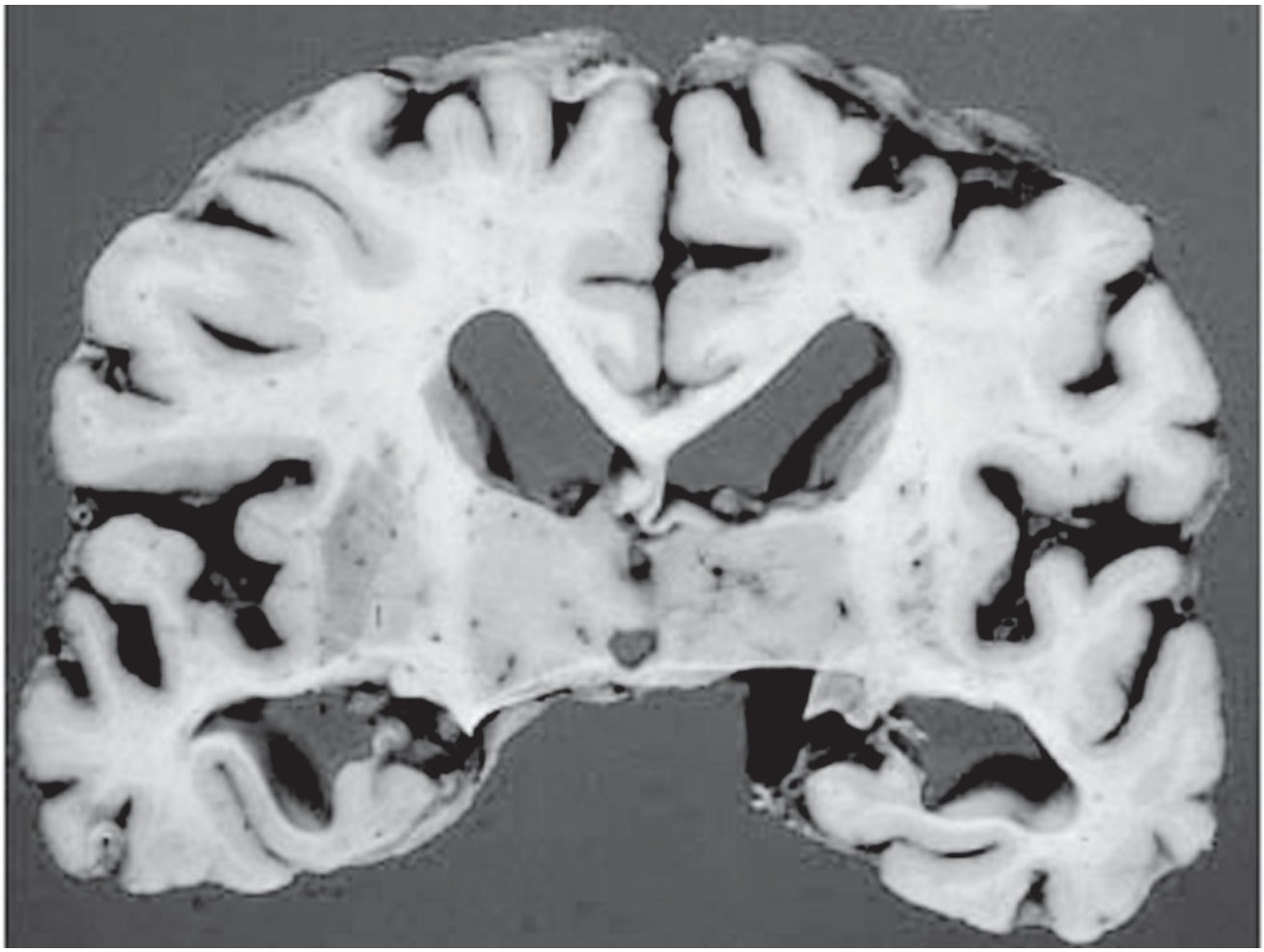

FIGURE 8–4. Coronal pathological section of a patient with confirmed Alzheimer disease. *(See color plate 6)* The section demonstrates hippocampal complex atrophy and dilatation of the temporal horn of the lateral ventricle.

Genetics

A very small proportion of Alzheimer disease cases (<5%) follow an autosomal dominant inheritance pattern. These individuals typically develop symptoms prior to age 55 years, with some experiencing symptoms as early as the fourth decade of life. Mutations on chromosomes 1, 14, and 21 are associated with up to 75% of all early-onset familial cases (Janssen et al. 2003). All of the known mutations result in excess production of Aβ. Another chromosome 21–related form of Alzheimer disease is found in individuals with trisomy 21 (Down syndrome) and occasionally in their relatives (Schupf et al. 2001). Instead of having a mutated gene, individuals with trisomy 21 possess three copies of the APP gene, probably resulting in production of excess Aβ, which overwhelms normal clearance pathways and leads to increased Aβ deposition (see also Chapter 24, "The Molecular and Genetic Basis of Alzheimer Disease").

Genetic epidemiology suggests that sporadic late-onset Alzheimer disease is best considered a complex genetic disease, with both genetic and environmental contributions. Twin studies, for example, suggest a concordance rate of only 20% in monozygotic twin pairs (Breitner et al. 1995). The ε4 allele of apolipoprotein E (APOE) is the genetic factor most clearly associated with increased risk for sporadic late-onset disease (Bertram et al. 2007). APOE is a lipid-carrying protein encoded on chromosome 19 that also binds to circulating Aβ. Other alleles of the APOE gene convey less risk and may even be protective. Numerous other putative risk factor loci have been identified, including sites on chromosomes 2, 9, 10, 12, and 15, but the specific genetic defects and the mechanisms by which these genes exert risk remain unknown (Bertram et al. 2007).

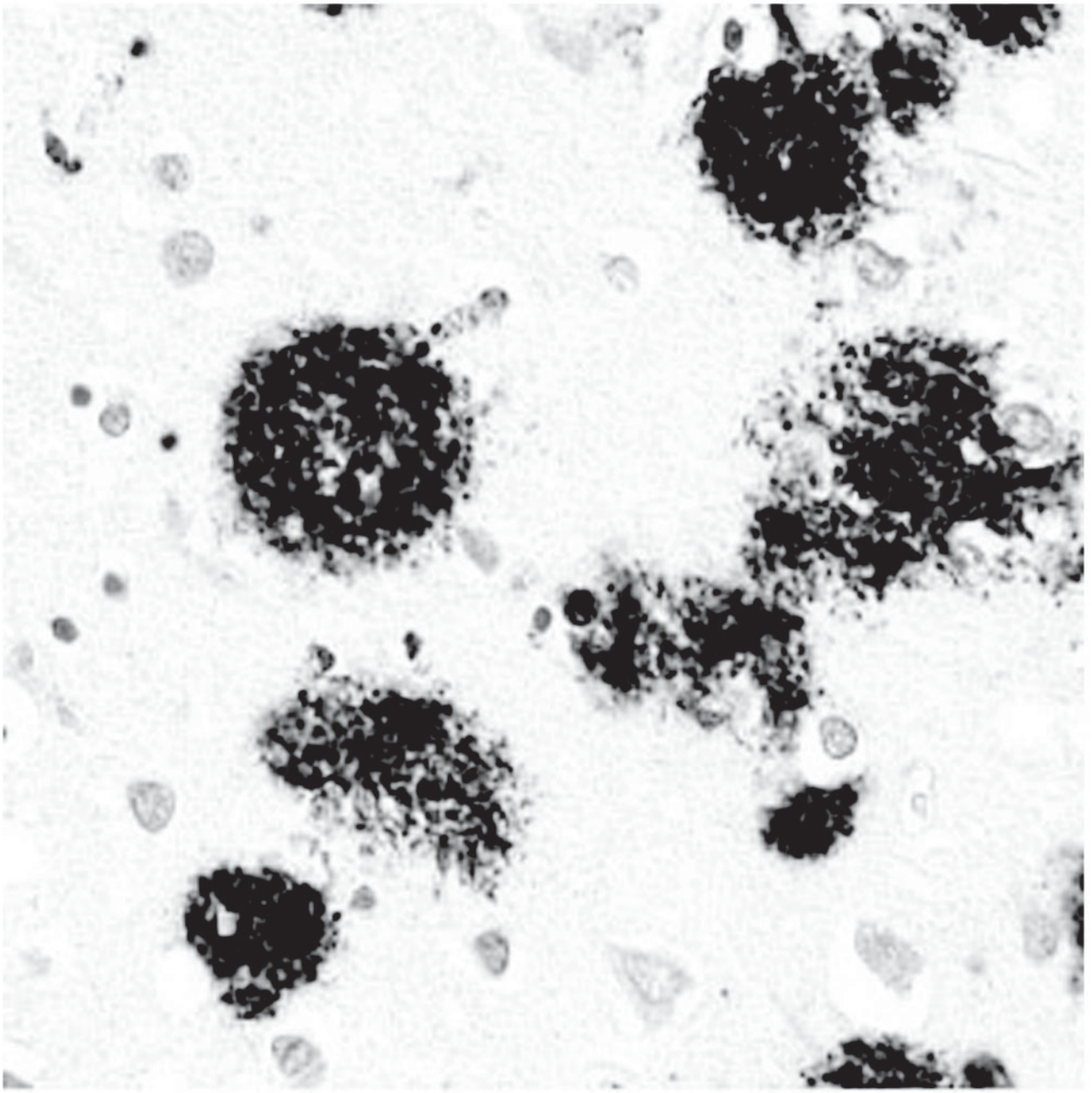

FIGURE 8–5. Photomicrograph of plaques in the cerebral cortex of a patient with Alzheimer disease. *(See color plate 7)* The section is immunostained for amyloid beta, which appears as dark extracellular granular material. The plaques are large compared to surrounding cellular nuclei.

Pathophysiology

Both APP and Aβ are normal neuronal protein products. Aβ is produced by the sequential proteolytic activities known as γ-secretase and β-secretase; the latter is also known as the β-amyloid cleaving enzyme (Stockley and O'Neill 2007). Functionally, γ-secretase activity appears to result from a transmembrane protein complex rather than a single enzyme (Verdile et al. 2007). Following β-secretase cleavage of APP, the action of γ-secretase produces the Aβ peptide, which normally ranges from 38 to 43 amino acids in length. A third enzyme known as α-secretase is also involved in normal APP processing. The cleavage site for α-secretase lies within the Aβ sequence and results in nonamyloidogenic products.

In Alzheimer disease, either an increased proportion of Aβ is produced, or there is reduced clearance of Aβ, or there is some combination of the two factors. In autoso-

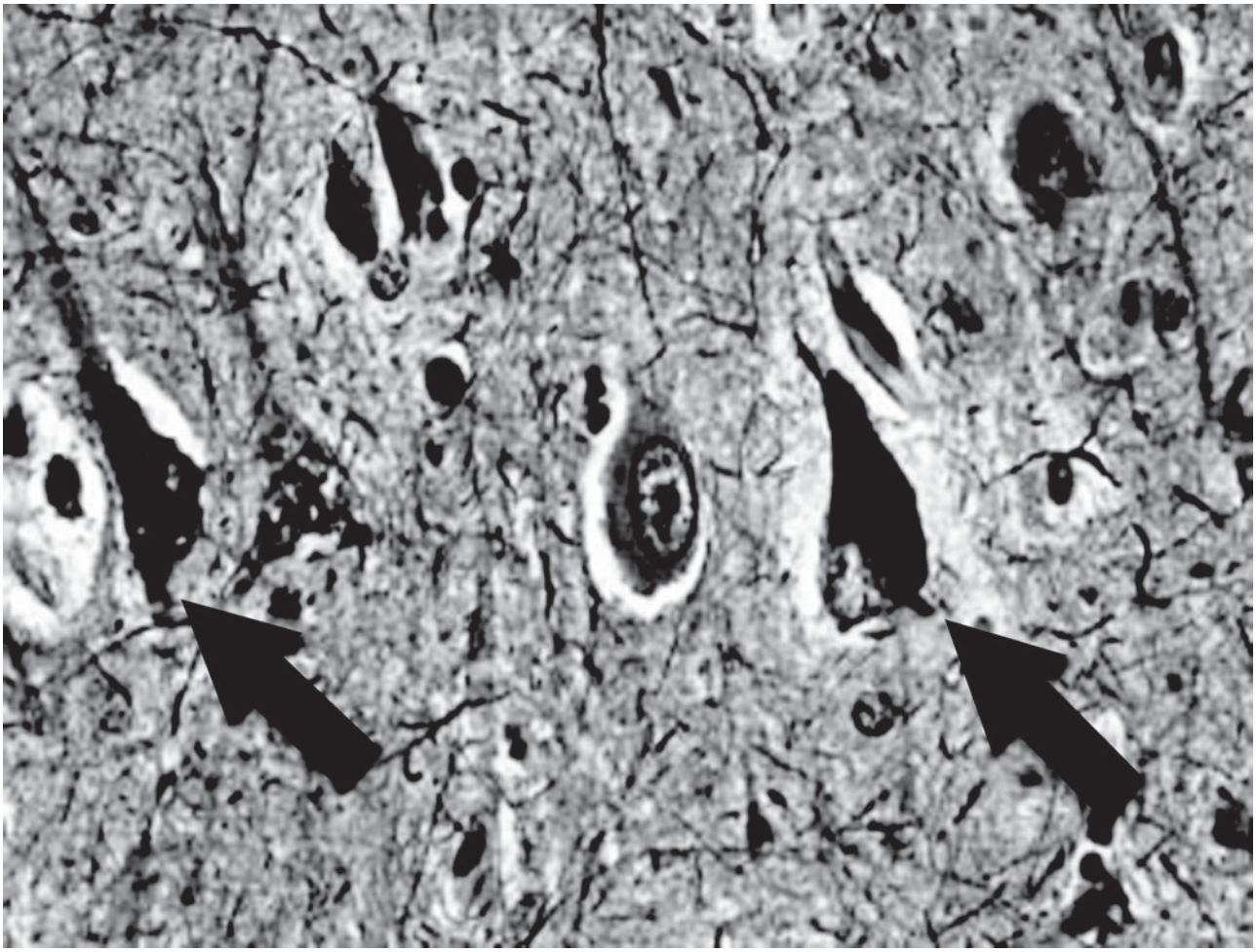

FIGURE 8–6. High-power photomicrograph of Bielschowsky-stained neurofibrillary tangles in the cerebral cortex of a patient with Alzheimer disease. *(See color plate 8)*
Tangles are intraneuronal and consist of collapsed cytoskeletal elements, including characteristic paired helical filaments. Tangle development interferes with normal neuronal function through loss of axonal transport and other vital homeostatic mechanisms.

mal dominant forms of the disease, mutations in and around the APP sequence or in sequences associated with the presenilin component of γ-secretase activity are associated with increased production of Aβ peptides. The 42 amino acid Aβ species is the most likely to associate into fibrils, which are the precursor to plaque formation. Fibrils aggregate into extracellular deposits in an insoluble β-pleated sheet configuration. Previously, parenchymal deposition of Aβ was assumed to be the crucial step in the Alzheimer disease pathophysiology. There is growing evidence, however, that prefibrillar, diffusible oligomeric assemblies of Aβ are toxic to neurons and synapses, suggesting that the disease process is under way well prior to plaque formation (Lacor et al. 2004). This concept is important because it raises the possibility of redefining the boundaries of the disease from both pathological and therapeutic perspectives.

The exact mechanism by which neuronal dysfunction and death occur in Alzheimer disease is unknown. Glycoproteins similar to APP are associated with cell surface interactions and nuclear signaling, suggesting that APP or its normal derivatives might play a role in maintaining synaptic function and neuronal health (Kamenetz et al. 2003). Aβ also acts as an activating trigger for microglial cells, leading them to produce several inflammatory cytokines, such as tumor necrosis factor-α, which have cytotoxic properties. Activation of microglia may contribute to a self-propagating cycle of local inflammation and neuronal dysfunction (Block et al. 2007). Although most models of Alzheimer disease pathophysiology place Aβ in a causative role, other approaches suggest oxidative stress or bioenergetic failure as triggering factors in the amyloid cascade (Swerdlow and Khan 2004). Alzheimer disease may in fact be a disorder with heterogeneous origins, with different primary mecha-

nisms resulting in similar patterns of neuronal failure and pathological expression in different individuals.

Neurochemical Abnormalities

Acetylcholine

Acetylcholine is important for the cognitive functions of attention and memory. Clinical disease severity correlates with loss of cerebral cortical markers for acetylcholine metabolism (Bierer et al. 1995). Choline acetyltransferase, responsible for acetylcholine synthesis, and acetylcholinesterase, which degrades acetylcholine, are both depleted. The degree of cholinergic reduction in the cortex is closely associated with the amount of cellular loss in the basal forebrain nuclei, where the neurons that produce much of the cortical acetylcholine are located.

Monoamines

Deficiencies in norepinephrine and serotonin also contribute to both cognitive and noncognitive symptoms, especially mood and anxiety symptoms. Norepinephrine is important for arousal, learning, and memory. The major site for norepinephrine production is the locus ceruleus in the brain stem, which undergoes significant cell loss in Alzheimer disease. Alzheimer disease is also associated with decreased markers of serotonin activity in the cortex and loss of serotonin-producing cells in the raphe nuclei of the brain stem (Lyness et al. 2003).

In the course of Alzheimer disease, intrinsic classical neurotransmitters, such as γ-aminobutyric acid (GABA), are also diminished, as are many cortically localized neuropeptides, such as somatostatin and corticotropin-releasing factor (Ellison et al. 1986; Panchal et al. 2004). The role of these changes in the clinical syndrome is unknown.

Glutamate and Other Transmitters

Conflicting evidence exists regarding the status of glutamate in the brain of a person with Alzheimer disease. Glutamate is the major excitatory neurotransmitter of the cerebral cortex, and neuronal markers of glutamate activity are generally decreased, especially in temporal cortex, in brains affected by Alzheimer disease (Ellison et al. 1986). However, some authors have reported that glutamate clearance from the synapse is diminished in more advanced Alzheimer disease. Residual synaptic glutamate is thought to result in overexcitation and dysfunction of postsynaptic neurons associated with excess calcium influx (Butterfield and Pocernich 2003). Direct human data on this hypothesis is limited. The role of these changes in the clinical syndrome is also unknown.

Treatment

Optimal treatment involves both pharmacologic and nonpharmacologic approaches (Doody et al. 2001). Currently approved therapies include members of the acetylcholinesterase inhibitor and *N*-methyl-D-aspartic acid receptor antagonist classes. These are generally considered symptomatic therapies and have not been demonstrated to alter the underlying pathological processes in Alzheimer disease. Treatment of behavioral symptoms is also symptomatically oriented (see Chapter 16, "Pharmacological Treatment of Neuropsychiatric Symptoms"), and no drugs have been specifically approved for this indication. Details of treatment outcomes are discussed in Chapter 18, "Pharmacological Treatment of Alzheimer Disease and Mild Cognitive Impairment."

KEY POINTS

- Alzheimer disease, alone or in combination with other pathology, is the most common cause of dementia in people over age 65 years.
- Diagnosis of Alzheimer disease requires impairment of memory and another cognitive domain, such as language, praxis, visual and spatial processing, or executive function.
- Noncognitive phenomena, including apathy and unawareness, are important contributors to the burden of Alzheimer disease.
- The general neurological examination is usually normal, although myoclonus may be present.

- Criterion-based diagnosis is very accurate, but no test short of pathological examination of the brain can definitively identify the presence of Alzheimer disease.
- Although the genetic basis of most cases of Alzheimer disease remains unknown, it appears to differ from the mechanisms underlying autosomal dominant, early-onset disease.
- Abnormalities in the processing of amyloid beta (Aβ) peptide contribute to the pathological expression of Alzheimer disease.
- Multiple neurotransmitter systems are affected, especially regulatory pathways involving acetylcholine and the monoamines.

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CHAPTER 9

Mild Cognitive Impairment

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Dementia is one of the leading global health problems (Chong and Sahadevan 2005). By the year 2050, an estimated 14 million people in the United States will have Alzheimer disease (Brookmeyer et al. 1998). The economic impact of Alzheimer disease is staggering; in 1993, the average cost of care for an Alzheimer patient in California was estimated to be over $40,000 per year (Rice et al. 1993). In view of this, devising a means of delaying the onset of dementing illnesses is a public health imperative. Prevention research depends in large measure on identifying a high-risk group suitable for interventional studies. One such group is persons with mild cognitive impairment (MCI) (Petersen et al. 1999).

MCI can be defined as the gray zone between normal cognitive aging and early dementia. Individuals with MCI show memory impairment greater than expected for their age but otherwise function independently and do not meet the commonly accepted criteria for dementia (Petersen et al. 2005).

History

Reisberg and colleagues, in 1988 and 1991 (Flicker et al. 1991), were perhaps the first to use the term *mild cognitive impairment* (Reisberg et al. 2008). Using the Global Deterioration Scale (Reisberg et al. 1982), they defined MCI as a score of 3 on a 7-point scale (1 = normal, 7 = severe dementia). The first attempt to characterize age-related memory concerns was made by Kral (1962), who used the term *senescent forgetfulness.* In 1986, the term *age-associated memory impairment* was proposed by an expert panel (Crook et al. 1986). Although introduction of the concept spurred research in the gray zone between normal cognitive aging and dementia, it had some limitations. For instance, age-associated memory impairment deals only with memory; the term is used to define individuals with a memory score at least one standard deviation below the

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mean for young adults. Using this criterion, and depending on the memory test selected, a rather large proportion of the elderly population would be labeled as impaired (Smith et al. 1991).

The International Psychogeriatric Association addressed these issues by creating the term *age-associated cognitive decline* (Levy 1994). The operational criteria referred to a variety of cognitive domains presumed to decline in normal aging and included age- and education-adjusted normative values. In addition to *age-associated memory impairment* and *age-associated cognitive decline*, other terms have been suggested (Blackford and LaRue 1989; Graham et al. 1997). On the Clinical Dementia Rating Scale (Morris 1993), for example, individuals with a score of 0.5 are in the category of "questionable dementia." However, many individuals with a Global Deterioration Scale score of 3 or a Clinical Dementia Rating Scale score of 0.5 may meet criteria for Alzheimer disease.

The Mayo Clinic criteria are widely used to define MCI. Mayo researchers incorporated advances made by theoretical constructs preceding their criteria. Also, Petersen et al. (1999) of the Mayo Clinic empirically validated the category of amnestic MCI in a prospective study. The Mayo criteria were also endorsed by the American Academy of Neurology. Studying MCI patients is important because this population develops dementia at 10%–15% per year, compared with 1%–2% per year in the general population (Petersen et al. 2001b).

Epidemiology

Little is known about the incidence or prevalence of MCI in elders. Some investigators have estimated the incidence rate to range from 1% to 6% per year and prevalence rate to range from 3% to 22% per year (Bennett et al. 2002; DeCarli 2003; Ganguli et al. 2004; Hanninen et al. 2002; Larrieu et al. 2002; Lopez et al. 2003).

The first population-based estimate of the prevalence of MCI and its subtypes was that of the Cardiovascular Health Study (Fried et al. 1991), in which the investigators retrofitted the criteria for amnestic and multidomain MCI to the cohort and reported an overall prevalence of MCI of 22%, with amnestic MCI accounting for 6% and multidomain MCI representing 16% in persons age 65 years or older (Lopez et al. 2003). More recently, an Australian research group estimated prevalence in a probability sample of individuals age 60–64 years; they reported much lower prevalence rates of 3.8% for MCI and 3.1% for age-associated cognitive decline (Kumar et al. 2005). Despite the researchers' excellent study design, by limiting the sample to a relatively younger age group, they likely underestimated the prevalence of MCI in that study.

In several studies, researchers have estimated the rate at which MCI progresses to dementia (Daly et al. 2000; Petersen et al. 1999, 2005; Tierney et al. 1996). Their findings vary depending on the study design and measurement instrument used (Dawe et al. 1992). For example, one group recruited study participants by advertisement, prospectively followed the cohort of subjects, and reported a conversion rate of 6% per year (Daly et al. 2000). In contrast, a clinical trial resulted in a conversion rate of 16% per year (Petersen et al. 2005). Earlier researchers reported conversion rates in the range of 10%–15%. Despite discrepancies across studies, all of the researchers pointed out that individuals with MCI developed dementia at a higher rate than did the general population. Thus, individuals with MCI constitute a high-risk group that is an optimal target for clinical trials.

One topic of debate and discussion is the "instability" of the MCI construct (Larrieu et al. 2002; Ritchie et al. 2001). French investigators reported a reversion rate from MCI to normal to be as high as 40% over 2–3 years; however, their sole MCI criterion was subjects' performance on the Benton Visual Retention Test (Benton et al. 1983). An international consensus panel on MCI has acknowledged that relying on poor performance on a single psychometric test may lead to a spurious conclusion about the instability of MCI. The panel emphasized the importance of progressive decline rather than results on one test at a single point in time (Winblad et al. 2004).

Clinical Features

Elderly individuals commonly present with memory concerns. Although such concerns may result from depression or the normal changes of aging, they may also indicate an early dementing illness. A typical clinical scenario follows.

Case 1

A 72-year-old right-handed man with 12 years of education presented with concern over forgetfulness for recent events and future engagements. Family members and close friends had made similar observations about him. The patient had difficulty identifying the onset of these symptoms but felt that they had started insidiously and progressed gradually over a period of 2–3 years. He was living independently and had no difficulty carrying out activities of daily living, such as handling his own finances, cooking, and driving. He denied depression, stress, or significant medical issues.

The clinical evaluation, which included history, physical examination, and brief cognitive screening, suggested that the patient had cognitive impairment, although not severe enough to warrant a diagnosis of dementia; hence, a tentative clinical diagnosis of MCI was made. Psychometric testing and a brain magnetic resonance imaging study were ordered. Neuropsychological testing revealed memory impairment, particularly on measures of learning and delayed recall, that was greater than expected for age; other cognitive domains such as language and visuospatial skills were relatively intact. The brain study revealed mild hippocampal atrophy.

The key finding from the patient's history is persistent, serious forgetfulness of insidious onset that gradually progressed over a year or so. This finding implicates the memory domain. All other cognitive domains, including language, executive function, and visuospatial skills, were intact. The individual did not have a decline in function. The patient was probably experiencing an early disease process involving information processing in the medial temporal lobe; the most likely diagnosis is amnestic MCI.

Subtypes

The original Mayo criteria for amnestic MCI are 1) a memory complaint, preferably corroborated by an informant; 2) impaired memory for age on psychometric testing; 3) normal general cognitive function; 4) intact activities of daily living; and 5) no dementia (Petersen et al. 1999). Although amnestic MCI is the most widely studied and empirically validated construct, an international consensus on MCI suggested three additional subtypes (Winblad et al. 2004). Figure 9–1 depicts the diagnostic algorithm that can be pursued to arrive at a diagnosis of a particular subtype of MCI.

The process has two major steps: establishment of the diagnosis of MCI, followed by identification of the type and number of cognitive domains involved. The algorithm is initiated when a patient or informant reports cognitive complaints such as forgetfulness for recent events and future engagements. The clinician then determines that the patient is neither demented nor normal for age. The next step is to make sure that there is no substantial decline in function via a careful history from the patient, which is corroborated by a collateral source. If the decline in function is not sufficient to warrant diagnosis of dementia, then the physician assumes the diagnosis of MCI and proceeds to identify the number and types of cognitive domains impaired.

Neuropsychological testing can be helpful in classifying MCI subtypes. A diagnosis of single-domain amnestic MCI is assumed if the impairment involves only memory, whereas multiple-domain amnestic MCI pertains to impairments in memory plus at least one other cognitive domain, such as language, executive function, or visuospatial skills. Likewise, a diagnosis of single-domain nonamnestic MCI is assumed if there is impairment in a single nonmemory domain, whereas multiple-domain nonamnestic MCI refers to impairments in multiple nonmemory domains.

The diagnostic algorithm shown in Figure 9–1 may be helpful in gaining more insight into the prodromal forms of dementia, which in turn may have therapeutic implications. Medications for treatment of prodromal forms of dementia may be specific to the underlying etiology of the developing disorder.

The single- and multiple-domain amnestic MCI subtypes with presumed degenerative etiology are probably prodromal Alzheimer disease (Winblad et al. 2004). The nonamnestic subtypes with impairments in the nonmemory domains have a higher likelihood of progressing to a non-Alzheimer dementia, such as dementia with Lewy bodies. Therefore, the combination of clinical subtypes and putative etiologies can be useful in predicting the ultimate type of dementia to which these diseases may evolve.

Neuropsychiatric Features

The neurological, psychometric, and neuroimaging aspects of MCI have been well studied, but relatively less work has been conducted in the neuropsychiatric aspect of MCI. Addressing neuropsychiatric features is quite logical because the medial temporal lobe and its connections with prefrontal and other structures play a critical role in both cognitive function and emotional behavior (Mesulam 1998). The first population-based investigation of the neuropsychiatric symptoms of MCI was reported by Lyketsos et al. (2002); this study was replicated by Geda et al. (in press) using the Mayo Clinic Population-Based Study of Aging. Since then, similar studies on this topic have been done using samples largely derived from primary or tertiary care settings (Feldman et al. 2004; Geda et al. 2004; Hwang et al. 2004). Psychiatric symptoms also were examined in prodromal Alzheimer disease (Copeland et al. 2003). Lyketsos et al. (2002) postulated that if MCI is a pre–Alzheimer disease state, the prevalence rate of neuropsychiatric symptoms in MCI should be intermediate between that of normal aging and dementia. Indeed, some findings substantiate that hypothesis (Geda et al. 2004; Hwang et al. 2004).

We prospectively followed a cohort of 840 cognitively intact elderly individuals for a median period of 3.5 years (range=1–15) to the outcome of incident MCI (Geda et al.

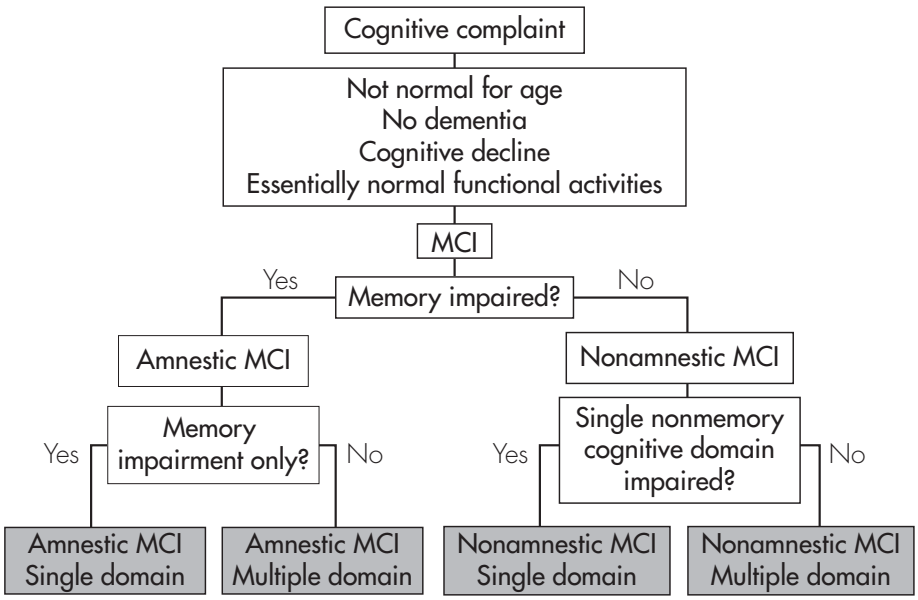

FIGURE 9–1. Flowchart of decision process for making diagnosis of subtypes of mild cognitive impairment (MCI).
Source. Courtesy of Ronald C. Petersen, Ph.D., M.D.

2006). We observed that depression, as measured by the abbreviated Geriatric Depression Scale (Sheikh and Yesavage 1986), more than doubled the risk of transition from normal aging to incident MCI. We also observed a synergistic interaction between depression and apolipoprotein E (APOE) genotype.

We proposed four hypotheses to explain the association between depression and incident MCI (see Figure 9–2). The first is an *etiological pathway*, in which depression leads to MCI via a neurobiological pathway wherein increased secretion of corticosteroids or other neurotoxic biological factors lead to brain damage. An implication of this hypothesis is that treating depression may help to prevent MCI.

The second hypothesis pertains to *shared risk factor or confounding*, wherein depression is associated in a noncausal way with an independent risk factor for MCI (Szklo and Nieto 2000). The risk factor could be genetic, environmental, or both. This hypothesis points to a susceptibility gene variant or another nongenetic risk factor that increases the risk of depression and MCI independently.

The third hypothesis is one of *reverse causality*. In this scenario, a person who is experiencing some degree of cognitive decline may develop depression as a reaction to the symptoms. The depressive symptoms may then "unmask" MCI in individuals with limited cognitive reserve. Thus, depression could be an early manifestation of preclinical MCI or a reaction to the initial symptoms of MCI.

Finally, an *interaction* may occur in which depression is a risk factor for MCI only in the presence of a susceptibility gene variant or another nongenetic risk factor. For example, we found evidence supporting a synergistic interaction between the *APOE* genotype and depression. We conducted analyses for interaction using, as the reference group, subjects who did not carry either ε3/ε4 or ε4/ε4 allele pairs and who did not have depression. Compared with the reference group, subjects with depression but no ε3/ε4 or ε4/ε4 allele pairs had a hazard ratio (HR) of 1.9 (95% confidence interval [CI], 0.9–4.1) for MCI, nondepressed subjects with ε3/ε4 or ε4/ε4 allele pairs had an HR of 1.6 (95% CI, 0.8–3.4), and subjects with both depression and ε3/ε4 or ε4/ε4 allele pairs had an HR of 5.1 (95% CI, 1.9–13.6).

Of course, these four mechanisms (and other possible mechanisms) are not mutually exclusive. Future studies based on these possible mechanisms could prove useful in understanding the psychiatric variables in MCI and in designing clinical trials that target psychiatric symptoms in the setting of MCI.

Neuroimaging

Although the cornerstone of MCI diagnosis is clinical, neuroimaging can have an important role in clarifying MCI diagnosis in a clinical setting. For example, magnetic resonance imaging (MRI) with visual qualitative and/or automated voxel-based morphometry may be helpful in predicting which subjects with MCI will progress to dementia. Early MRI work was limited mainly to measure-

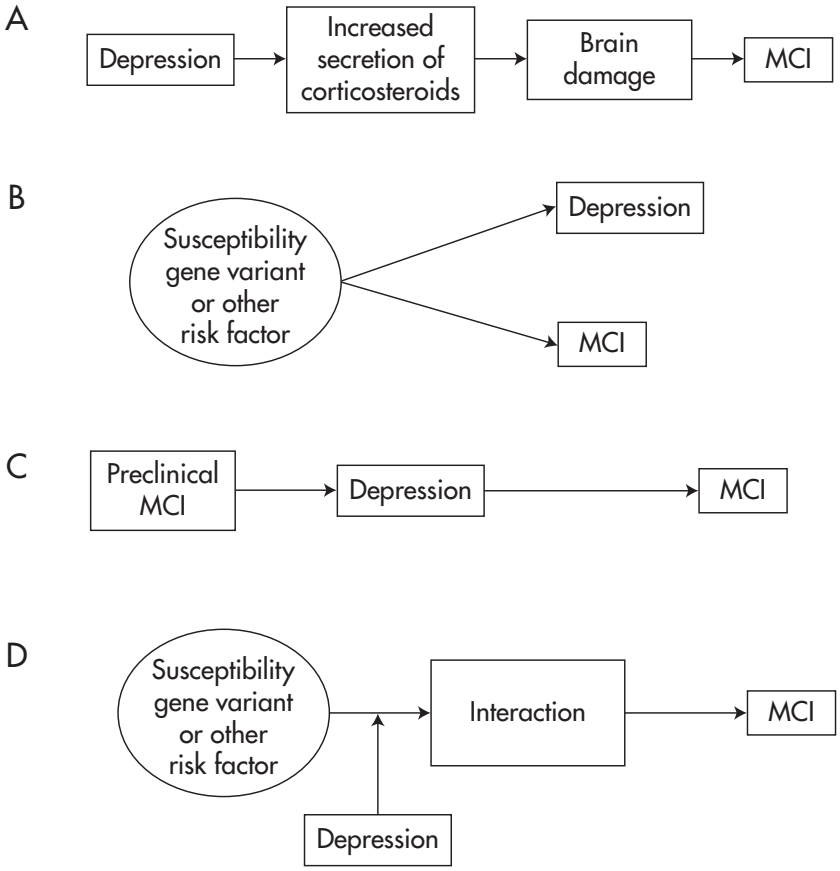

FIGURE 9–2. Four possible mechanisms linking depression to mild cognitive impairment (MCI).
(A) Etiological pathway; (B) shared risk factor or confounding; (C) reverse causality; (D) synergistic interaction.
Source. From Geda YE, Knopman DS, Mrazek DA, et al: "Depression, Apolipoprotein E Genotype, and the Incidence of Mild Cognitive Impairment: A Prospective Cohort Study." *Archives of Neurology* 63:435–440, 2006. Copyright 2006, American Medical Association. Used with permission.

ment of the hippocampal volume, but as imaging research has progressed, atrophy of the entorhinal cortex has been identified as an early marker of amnestic MCI and a predictor of the future development of Alzheimer disease. An important challenge in MRI research is variability in methods of measuring hippocampal volume, but a recent study suggests that subjective visual assessment of hippocampal volume can be useful (DeCarli et al. 2007). Diffusion weighted imaging and magnetic resonance spectroscopy have been reported to be useful techniques in the neuroimaging of MCI (Kantarci et al. 2004, 2005).

Investigations using functional MRI (fMRI) have reported positive correlations between performance on memory tasks and medial temporal lobe or hippocampal activation (Dickerson et al. 2004). The increased activation of the right parahippocampal gyrus, which was observed with increasing clinical impairment, was interpreted as being suggestive of recruitment of additional networks and structures to compensate for the amnestic difficulties in these patients. Research using fMRI studies of MCI has found increased activation or recruitment of several other structures, such as the frontal, temporal, anterior cingulate, and fusiform gyri. These activations have been interpreted as compensatory networks by some investigators. However, decreased activation has been observed in anterior frontal, prefrontal, precuneus, and posterior cingulate gyri as well. The enthusiasm for investigations involving fMRI is tempered by methodological and technological limitations. When fMRI is used to compare control subjects and MCI cases, verbal tasks cannot be used to measure memory and encoding because of motion artifact. Therefore, visual rather than verbal memory tasks are used. However, verbal tasks would be preferable because they are clinically more sensitive to early changes in MCI. A clearer understanding of normal variability and age-related changes that appear in fMRI will enable researchers to better use fMRI to understand disruption of neural systems in MCI.

Reduced cerebral perfusion and glucose metabolism (as measured by single photon emission computed to-

mography [SPECT]) and decreased glucose metabolism (as measured by positron emission tomography [PET]), in temporoparietal regions, the posterior cingulate gyrus, and the hippocampus regions have been associated with progressive cognitive decline in MCI; however, these changes lack sensitivity and specificity for MCI (Chételat et al. 2003) . A study investigated metabolic activity in the hippocampi of subjects with MCI using both the region-of-interest technique and voxel-based analysis; it reported hypometabolism in the hippocampi of subjects with MCI, but this was evident only with the region-of-interest technique and not with voxel-based analysis (Mosconi et al. 2005). The limitations in spatial resolution in PET and deformation of brain areas in voxel-based analysis were proposed as likely explanations for the discrepant findings in this study and others.

At the University of Pittsburgh, Klunk and colleagues have developed a marker known as Pittsburgh Compound B (PIB), which enables in vivo imaging of brain amyloid (Klunk et al. 2003, 2004). The potential of this marker for detecting incipient or preclinical Alzheimer disease has led to tremendous enthusiasm in the research community. Klunk and colleagues used PIB to evaluate five cognitively healthy control subjects, five individuals with MCI, and five patients with Alzheimer disease. Using this technique, they were able to distinguish individuals with Alzheimer disease from control subjects; however, rather than exhibiting the expected transitional or intermediate state of PIB retention, the MCI cases either were similar to the Alzheimer cases or appeared normal. This finding may reflect that MCI is a heterogeneous condition. Incident MCI cases might resemble normal controls, whereas advanced MCI cases might resemble Alzheimer disease.

Neuropathology

A question that often arises is whether persons with MCI actually have Alzheimer disease at the time they are clinically diagnosed with MCI. This is a reasonable question because many biomarker and neuroimaging studies have indicated that the Alzheimer disease process is well under way even at the MCI clinical stage. Recently, two studies addressing this issue were completed by investigators at the Mayo Clinic. One study indicated that individuals who died while their clinical classification was amnestic MCI actually did not meet criteria for the neuropathological diagnosis of Alzheimer disease (Jicha et al. 2006). Rather, most of the subjects studied appeared to have transitional pathology, which implied that had they lived longer, they would have developed the full neuropathological picture of Alzheimer disease. However, when they died, there were insufficient data to conclude that they had Alzheimer disease. The most common characteristics of these subjects included neurofibrillary pathology in the medial temporal lobe and diffuse amyloid deposition in the neocortex. Most of the subjects did not have sufficient neuritic plaque pathology to constitute Alzheimer disease neuropathologically.

Another study followed subjects who had previously been diagnosed with MCI and subsequently progressed to dementia (Petersen et al. 2006). This study revealed that although most of the subjects with amnestic MCI went on to have Alzheimer disease clinically and pathologically, over 20% did not. This finding indicates that although the amnestic MCI criteria are reasonably specific, they are not sufficiently specific that the diagnosis of Alzheimer disease can be made definitively at this clinical state. Some of the subjects went on to have other forms of dementia, such as dementia with Lewy bodies, frontotemporal dementia, or vascular dementia. This variability raises the issue of specificity of the clinical criteria such that most but not all subjects at the MCI stage are likely to progress to Alzheimer disease. Consequently, because clinicians need to be as accurate as possible and not mislabel subjects with Alzheimer disease, it is preferable to retain the diagnosis of MCI with its qualifications with regard to longitudinal outcome.

Treatment

MCI has no standard treatment, but numerous clinical trials are being undertaken with the aim of delaying the onset of dementia (Chertkow 2002). These trials, which have been reviewed comprehensively by Geda and Petersen (2001), have included acetylcholinesterase inhibitors, vitamin E, and piracetam and nonsteroidal anti-inflammatory agents in studies with durations of 6 months to 3 years. A large clinical trial involving 70 medical centers in North America was recently reported (Petersen et al. 2005). It was a randomized, double-blind, placebo-controlled study to assess the safety and efficacy of vitamin E (2,000 IU per day) and donepezil (10 mg per day) and was powered to detect a decrease in the conversion rate of MCI to Alzheimer disease from the anticipated 45% down to 30% over the course of 3 years. Among the 769 subjects randomized, the annual conversion rate from MCI to Alzheimer disease was approximately 16% per year (48% over 3 years). Donepezil reduced the risk of progressing to Alzheimer disease for the first 18 months of the trial. Vitamin E had no therapeutic effect.

KEY POINTS

- Amnestic MCI seems to be an intermediate stage between normal aging and Alzheimer disease.
- Amnestic MCI is associated with biological markers such as decreased hippocampal volume and the accumulation of amyloid plaques in the brain.
- Other forms of MCI may be related to other types of brain pathology.
- Neuropsychiatric symptoms are more prevalent in subjects with MCI than in age-matched cognitively healthy controls.

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CHAPTER 10

Vascular Cognitive Disorder

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During the twentieth century, the most commonly used term for vascular-type cognitive change was *vascular dementia*. The main limitation of this term is its exclusion of patients with cognitive deficits but no memory impairment. Similarly, criticism of the term *vascular cognitive impairment* relates to the fact that it appears to exclude those with established dementia due to the ambiguity of the word *impairment*. Hence, we use the term *vascular cognitive disorder* in this chapter to represent the wide diversity of vascular changes that can lead to cognitive impairment and dementia.

Vascular cognitive disorder is a constellation of syndromes related to different vascular mechanisms. A key factor with this form of cognitive impairment is that vascular changes are to some extent preventable. Therefore, early detection and accurate diagnosis with development of appropriate treatments and risk factor control can have a significant impact.

History

Progress in understanding the etiology and treatment of vascular cognitive disorder has been limited by difficulties with terminology and the variability of its clinical presentation. Only recently has it been recognized as a significant cause of dementia within the community. Although initial work in dementia routinely attributed cognitive damage to arteriosclerosis and chronic cerebral ischemia, the discovery of Alzheimer disease changed this view and largely eclipsed vascular cognitive disorders. With Alzheimer disease seen as the major cause of dementia, the criteria to assess this disease formed the basis of all dementia diagnosis (American Psychiatric Association 1994; McKhann et al. 1984; World Health Organization 1992). The subsequent focus on memory impairment being the defining event leading to a diagnosis of dementia has over-

shadowed the significance of damage to other equally important cognitive domains.

Observations from antiquity describe cognitive decline following "apoplexy." Dementia after stroke was reported by Thomas Willis in the seventeenth century. The contribution of vascular damage to cognitive change was first described as early as the 1800s. In 1899, arteriosclerosis and senile dementia were delineated as distinct syndromes, with older dementia patients thought more likely to have the vascular type (Holstein 1997). Later, however, histological studies in older patients with dementia revealed predominantly Alzheimer pathology, which temporarily removed the view that vascular disease played a significant role in this group (Nolan et al. 1998). It was not until new histopathological techniques became available in the late nineteenth century that a clear differentiation between the circulatory and degenerative etiologies of dementia was described. A renewed interest in vascular etiologies occurred in the late 1960s, when a strong association between hypertension, arteriosclerosis, and dementia was reported (Román 2003). Hachinski described multi-infarct dementia in 1974, a condition now recognized as a subtype of vascular dementia. More recently, the association between vascular disease and characteristic findings in patients with Alzheimer disease was recognized. An improved understanding of the metabolic, chemical, and neurogenic control of cerebral blood flow and metabolism (Edvinsson et al. 1993) and advances in neuroimaging have led to a resurgence of interest in vascular cognitive disorder.

Diagnostic Criteria

Vascular cognitive disorder encompasses vascular dementia, vascular cognitive impairment without dementia, and mixed Alzheimer and cerebrovascular dementias (Bowler 2002). Although vascular cognitive disorder was first described in 1985, its expansion to include rather than to be a subset of vascular dementia occurred only recently. Debate continues because the term implies an absence of dementia, and therefore *vascular cognitive disorder* may be the most appropriate term (Román et al. 2004). These difficulties with definitions have arisen because of the wide spectrum of clinical syndromes that can occur with vascular pathology. Just as strokes located within different regions of the brain can produce highly variable symptoms, the cognitive effects from lesions of different types and at different locations vary enormously. Stroke physicians have recognized a number of syndromes that have specific outcomes, treatment options, and prognoses. A similar mechanism of damage can result in a range of deficits in cognitive, behavioral, and executive functions, and therefore appropriate syndromal classification can have important implications for management.

Development of Diagnostic Criteria

Although initial diagnostic criteria have been superseded, a review of the history of vascular dementia classification is important because much of the earlier research relied on these criteria. A variety of terms and scales have been used. The term *dementia of the cerebrovascular type* was limited by its exclusion of cardiac or hypotensive causes of cerebral ischemia. The term *multi-infarct dementia* was accompanied by a scale to aid in diagnosis (Hachinski et al. 1975). This model made clear distinctions between Alzheimer disease and multi-infarct vascular cognitive disorder, but it did not account for those individuals with cognitive change from one single event or from progressive insidious small vessel damage.

Dementia is defined in DSM-IV-TR (American Psychiatric Association 2000) as a syndrome of acquired intellectual deficits that results in significant impairment of social or occupational functioning. DSM-IV, ICD-10 (World Health Organization 1992), and NINDS-AIREN criteria (Román et al. 1993) require the presence of memory impairment. Although the early involvement of the medial temporal lobes in Alzheimer disease leads to almost universal early involvement of memory, memory may be only slightly impaired in cerebrovascular disease. Thus, patients who are unable to care for themselves due to severe visuospatial and executive dysfunction are not diagnosed as having a dementia. For a diagnosis of dementia, ICD-10 criteria require two or more other cognitive domains to be involved, whereas DSM-IV criteria permit inclusion of a more focal dementia type.

The most widely used diagnostic criteria for vascular dementia, particularly in research trials, have been the NINDS-AIREN consensus criteria, presented in Table 10–1. These criteria, although based on the ICD-10 dementia diagnosis, also address 1) pathological subtypes of vascular dementia syndromes and 2) the variability in the clinical course as not necessarily always being stepwise but potentially static, remitting, or progressive. The NINDS-AIREN criteria also stress the importance of specific clinical findings and of neuropsychological assessment to distinguish vascular dementia from classical Alzheimer-type dementia based on deficits in cognitive domains other than memory. The criteria also established the importance of brain imaging. The temporal relationship between the appearance of a new cortical stroke or

TABLE 10–1. NINDS-AIREN criteria for the diagnosis of vascular dementia

I. The criteria for the clinical diagnosis of *probable* vascular dementia include *all* of the following:
   1. *Dementia* defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
   2. *Exclusion criteria:* cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as Alzheimer's disease) that in and of themselves could account for deficits in memory and cognition.
   3. *Cerebrovascular disease*, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of not relevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter lacunes*, or *extensive periventricular white matter lesions*, or combinations thereof.
   4. *A relationship between the above two disorders*, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of *probable* vascular dementia include the following: (a) Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); (b) history of unsteadiness and frequent, unprovoked falls; (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease; (d) pseudobulbar palsy; and (e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include (a) early onset of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging; (b) absence of focal neurological signs, other than cognitive disturbance; and (c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of *possible* vascular dementia may be made in the presence of dementia…with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of *definite* vascular dementia are (a) clinical criteria for *probable* vascular dementia; (b) histopathologic evidence of CVD obtained from biopsy or autopsy; (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and (d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.
The term "AD *with* CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD in epidemiologic studies. The term "mixed dementia," used hitherto, should be avoided.

Note. ACA = anterior communicating artery; AD = Alzheimer disease; BD = Biswanger disease; CT = computed tomography; CVD = cardiovascular dementia; MRI = magnetic resonance imaging; PCA = posterior communicating artery; VaD = vascular dementia.

Source. Reprinted from Román GC, Tatemichi TK, Erkinjuntti T, et al: "Vascular Dementia: Diagnostic Criteria for Research Studies. Report of the NINDS-AIREN International Workshop." *Neurology* 43:250–260, 1993. Used with permission.

progression of white matter disease and change in cognitive function was recognized. In regard to neuroimaging, the NINDS-AIREN criteria were the first to include specific criteria to describe both location and severity of lesions (Román et al. 1993), which are used to reach a diagnosis of *probable* vascular dementia (memory impairment + another cognitive domain + cerebrovascular disease imaging evidence with clear association to decline) or *possible* vascular dementia (memory impairment + another cognitive domain + cerebrovascular disease without imaging evidence or clear association to decline). These criteria are now the most widely used because they provide a clear standard with a pathophysiological basis and have high specificity. They remain limited, however, by the essential requirement of memory impairment.

None of the current criteria for vascular dementia includes individuals with intact memory whose executive dysfunction is severe enough to impair daily functioning. Nor do they include those people with vascular cognitive impairment or mild vascular cognitive disorder, although it is these patients who are at risk of significant progression and comorbidity from their vascular risk factors and are most likely to benefit from identification, early intervention, and therapy.

Comparison of Scales and Diagnostic Criteria

Since the NINDS-AIREN criteria were first published, additional studies have revealed that they have low sensitivity (Chui et al. 2006; Reed et al. 2007). The Hachinski et al. (1975) scoring paradigm, originally developed to study cerebral blood flow patterns in dementia patients, was composed by listing typical features of vascular dementia from a textbook of neurology. Despite its lack of prior validation, it has been a reliable means of identifying patients with vascular dementia. Further validation has resulted in a scale with sensitivities and specificities of approximately 80% (Katzman et al. 1988). Numerous attempts have been made to develop criteria. These criteria are often developed for clinical research, where high specificity is the priority, but clinical use continues to be limited by low sensitivity.

Of the criteria available, the Hachinski scale has the highest interrater reliability, the DSM-IV-TR criteria have the best sensitivity (50%), and the NINDS-AIREN criteria have the highest specificity (97%) (Chui et al. 2000). In addition to assessing the clinical performance of the criteria, researchers have conducted postmortem studies comparing clinical diagnoses with pathological findings. Gold et al. (1997) examined 113 autopsy-confirmed cases of dementia. Application of diagnostic criteria revealed that the Hachinski scale had 88% specificity and the NINDS-AIREN criteria had 80% specificity. The highest sensitivity (63%) was achieved by the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria (Amar et al. 1996). However, autopsy studies are limited by the difficulty in identifying extensive small vessel disease without clear lacunar infarcts, although this combination would be uncommon in a population of individuals who died with vascular dementia. Additional limitations of autopsy studies are the lack of validated pathological criteria for vascular dementia. Therefore, criteria used in the studies by Gold et al. (1997) and Amar et al. (1996) were the absence of Alzheimer pathology and the presence of vascular changes.

Although the NINDS-AIREN criteria have adequate specificity for vascular dementia (93% for probable, 84% for possible) and poor sensitivity (20% for probable, 55% for possible) (Gold et al. 2002), this low sensitivity indicates that a large proportion of cases of vascular dementia are not detected by the current classification system. Another limitation of the criteria is in their application. When the DSM-IV, NINDS-AIREN, and ADDTC criteria were all used to classify a large subset of patients with incident dementia from the Cardiovascular Health Study, the different criteria identified entirely different subjects (Lopez et al. 2005). Similar results were seen with a study of nearly 1,900 patients enrolled in the Canadian Study of Health and Aging, in which a tenfold difference was seen in the incidence of vascular dementia depending on the classification used (Erkinjuntti et al. 2007).

The greatest limitation of the NINDS-AIREN criteria is their reliance on imaging. Strict application of the imaging criteria to poststroke patients showed no difference in findings between those with and those without dementia, with a greater degree of hippocampal atrophy being the only distinguishing feature of those with dementia (Ballard et al. 2004). Therefore, the possibility exists that some cases of poststroke dementia may represent an unmasking of preexisting Alzheimer pathology.

In addition to the low sensitivity of current diagnostic criteria, they do not detect cases of mixed vascular and Alzheimer pathology. Because an overlap of up to 40% occurs between vascular and neurodegenerative dementias (Kalaria and Ballard 1999), it is surprising that no diagnostic criteria include mixed-type dementia. Gold et al. (2002) estimated that up to 50% of mixed dementia cases are classified as "pure" vascular cognitive disorder. Even the reliability of autopsy studies has to be questioned when the incidence can vary from 0% to 55% (Zekry et al. 2002). The complexity of multifactorial pathology is increased by the fact that vascular lesions in the centers involved in memory (basal ganglia, thalamus, or deep white

matter) have the ability to significantly worsen the symptoms of Alzheimer disease (Snowdon et al. 1997).

Summary of Classifications and Diagnostic Scales and Criteria

The most significant limitation of current classification systems is their low sensitivity. The variability in criteria across all of the commonly used systems can mean that the same patient will receive different diagnoses depending on the system used. This variability causes difficulty with research and makes the comparison of some cohorts impossible, as well as brings into doubt the basis for many of the distinctions made. An ideal classification system would make full use of the increasing availability of magnetic resonance imaging (MRI), would take into account functional brain imaging, and would not have memory impairment as a primary requirement for diagnosis.

Vascular Cognitive Disorder

Vascular cognitive disorder is diagnosed based on imaging, history, or examination evidence that cerebrovascular disease is responsible for the cognitive impairment. Memory impairment, if present, is characteristically of the nonamnestic type (i.e., inefficiency in both initial registration and recall of information, with recall of established memory often similarly affected). The term *vascular cognitive impairment* is used when there is cognitive decline with intact functional ability. The term *vascular dementia* is used when the severity of cognitive deficits is sufficient to impair the patient's ability to live independently.

The subtypes of dementia discussed in the following sections overlap with pathophysiological systems, with classification based on the underlying etiology. The three main contributors to vascular-type dementia are localized infarction, microvascular disease, and concurrent atrophy. Improved classification can augment the capacity to study phenotypes, allowing a better understanding of the pathophysiology of disease and a determination of the most appropriate treatment.

Subcortical Ischemic Vascular Cognitive Disorder

The most common form of vascular cognitive disorder is thought to be subcortical vascular damage. Given that lacunar stroke represents 20%–30% of symptomatic stroke, this subtype of vascular cognitive disorder is likely to be highly prevalent in the aging population. The hypothesis is that small lacunes cause a loss of subcortical neurons or that the disconnection of these neurons from the cortical neuronal pathways causes the constellation of dysexecutive syndrome, slowed cognition and motor processing speed, and attentional impairment. Memory deficits in this disorder generally consist of impaired recall of both recent and distant information, with relatively intact recognition. Neuroimaging reveals lacunar infarctions and deep white matter changes.

The pattern of cerebral damage in subcortical ischemic vascular cognitive disorder is caused by diffuse small vessel disease. Clinical features, which depend on the location of lacunar lesions, often include frontal lobe signs (especially impairment of executive function), global cognitive decline, and affective symptoms. These clinical features have been linked to cerebral blood flow abnormalities in frontal areas and basal ganglia (Yang et al. 2002), and these patients are at high risk of developing secondary depression.

Multi-Infarct Vascular Cognitive Disorder

In patients with multi-infarct vascular cognitive disorder, structural imaging reveals evidence of strokes or white matter infarcts. Evidence of development of focal neurological signs across examinations or evidence of an increased burden of cerebral ischemia on brain imaging is temporally associated with the cognitive decline. This subtype is often described as having a stepwise decline.

Vascular Cognitive Disorder Due to Strategic Infarcts

In patients with vascular cognitive disorder due to strategic infarcts, the degree of cognitive decline is out of keeping with the overall vascular burden. The strategic location of infarcts interferes maximally with memory and cognition, as in cases of anterior cerebral artery infarcts, parietal lobe infarcts, cingular gyrus infarction, and particularly thalamic infarction.

Diffuse White Matter Disease

Some patients with cognitive decline have diffuse white matter disease (leukoaraiosis) that is evident on neuroimaging. Several large studies have reported the correlation of leukoaraiosis and cognitive decline (Longstreth et al. 2005; Prins et al. 2005; Schmidt et al. 2004; van den Heuvel et al. 2006). The syndrome of Binswanger disease is a specific subtype of diffuse subcortical leukoencephalopathy that is due to thickening of the walls of the small arteries and fibrinoid necrosis of the larger vessels inside the brain (Yao and Sadoshima et al. 1992). The associated vasculopathy, aneurysm formation, and stenosis in the leptomeningeal and cortical vessels cause damage to the sub-

cortical white matter. The occurrence of other dementia subtypes has not been prevalent enough to be recognized as syndrome.

Vascular Cognitive Disorder Due to Hemorrhagic Lesions

Vascular cognitive disorder due to hemorrhagic lesions, or amyloid angiopathy, involves the accumulation of amyloid within the walls of cerebral blood vessels. This buildup can cause bleeding and interruption of cerebral blood flow. This disorder is sometimes caused by hereditary conditions. For example, patients with hereditary cystatin-C amyloid angiopathy have recurrent cerebral hemorrhages, which can lead to dementia, before age 40 years (Harkness et al. 2004).

Inflammatory Vascular Disease

Rare arteriopathies can cause multiple infarcts and vascular cognitive disorder. Arteriopathies can be inflammatory (polyarteritis nodosa, temporal arteritis) or noninflammatory (moyamoya disease, fibromuscular dysplasia).

Hypoperfusion

Hypoperfusion due to large vessel or cardiac disease can affect the watershed areas of the brain, leading to vascular cognitive disorder. This condition can be seen in states of low cardiac output such as severe congestive heart failure or decreased cerebral flow from any other cause.

Mixed Alzheimer and Vascular Dementia

A diagnosis of mixed dementia is based on history and typical neuropsychological findings of Alzheimer disease and evidence of cerebrovascular disease, either clinically or based on neuroimaging evidence of ischemic lesions. Mixed dementias are the most recently described subtype of dementia, and the proportion of individuals diagnosed with this condition rather than another subtype of dementia will likely increase (Schneider et al. 2007).

Epidemiology

The incidence of vascular dementia is about 1.3 per 100 individuals over age 65 years per annum (Solfrizzi et al. 2004). Whereas Alzheimer disease is reportedly more common in Western countries, vascular dementia is more common in Japan, China, and Russia (Jorm and Jolley 1998; Jorm et al. 1987). A Swedish study reported a lifetime risk of developing vascular dementia as 34.5% for men and 19.4% for women (Hagnell et al. 1992). Vascular dementia may be the second most common type of dementia, with 10%–20% of people with late-onset dementia having evidence of this type (Rocca et al. 1991). The high prevalence of vascular lesions in patients diagnosed with Alzheimer disease, however, has led many to suggest that mixed Alzheimer and vascular dementia is in fact the most common type of dementia in developed countries (del Ser et al. 1990). When younger than age 75 years, men are at higher risk for vascular-type dementia, and women are at higher risk for Alzheimer-type dementia; in older age, the sex difference is less pronounced (Jorm and Jolley 1998). Dementia is common in those who suffer stroke, either immediately after stroke or with delayed onset (Leys et al. 2005). Although the risk of developing dementia increases with age. the prevalence of vascular dementia increases less steeply than that of Alzheimer disease.

The overlap between vascular cognitive disorder and ischemic stroke has been the source of much phenotypic confusion. Ischemic stroke was initially divided into large and small vessel disease, whereas vascular cognitive impairment was initially divided into cortical and subcortical types, although more recently these diagnostic criteria have been revised (Kidwell and Warach 2003; Wetterling et al. 1996). The location of the infarct is the most significant determinant of poststroke dementia. After age 65 years, one-third of people who have had a stroke will manifest vascular dementia (Esiri et al. 1999).

Genetics

As with most complex disease states, monogenic conditions represent only a minority of cases of vascular cognitive disorder. The discovery of vascular types of monogenic dementia, despite their rarity, can provide enormous insight into the pathophysiology of the disease, as well as important directions for treatment. The angiopathies are also important genetic disorders that predispose individuals to both stroke and vascular cognitive disorder. Certain familial forms of dementia related to homocystinuria and types of amyloidosis have been described (Adair et al. 1998; Adam et al. 1982). In vascular dementia, no significant difference in concordance rates occurs among monozygotic and dizygotic twin pairs (Bergem et al. 1997); these findings suggest that environmental factors play a large role. Population-based genetic screening has not been successful in discovering a clear genetic risk factor for developing vascular cognitive disorder. Association

with apolipoprotein E polymorphisms has shown conflicting results (Gorelick 1997).

Some rare genetic disorders result in cerebral ischemic damage, the best described being cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; Dichgans 2002) and autosomal dominant hereditary cerebral hemorrhage with amyloidosis (Bornebroek et al. 1996, 2003; Ghiso et al. 1986; Luyendijk et al. 1988; Majersik and Skalabrin 2006; Nishitsuji et al. 2007; Remes et al. 2004; Wang et al. 1997). CADASIL, a rare autosomal dominant condition localized to chromosome arm 19q12, affects small vessels supplying the deep white matter; pathologically, multiple small infarcts are observed predominantly in the white matter, thalamus, basal ganglia, and pons.

Leukoaraiosis has evidence for genetic risk, with twin studies revealing a heritability of 71% and genome-wide scanning showing strong linkage on chromosome 4p (DeStefano et al. 2006). The area on 4p has no previously identified stroke risk factor genes but is known to contain aging- and mitochondrial-related genes.

Etiology

An important consideration in the etiology of vascular cognitive disorder is its large overlap with aging. In advanced age, the reduction in cognitive reserve means that a smaller lesion can result in clinically significant dementia. In addition, other factors associated with aging, such as vitamin (vitamin B_{12}, folic acid) deficiency leading to hyperhomocysteinemia and end organ dysfunction (particularly cardiac), can predispose to dementia. Vascular disease can cause both focal and diffuse effects on the brain. Whereas focal disease is most likely to result from large vessel pathology secondary to thrombotic or embolic vascular occlusions, hypertension is the main cause of diffuse disease from small vessel pathology.

Brain parenchymal damage of vascular origin can occur from ischemia, hemorrhage, or edema. The main types of damage result from one or a combination of single strategic infarcts, multiple infarcts, lacunae, small vessel disease, or diffuse white matter disease. The areas of the brain that when damaged cause cognitive impairment are the white matter of the cerebral hemispheres and deep gray nuclei (striatum and thalamus). Complex feedback loops occur in the pathophysiology of vascular cognitive disorder. Hypertension, diabetes, and cardiac disease predispose to vascular events. Although the various subtypes of vascular lesion can coexist, we address their etiology separately.

Macrovascular Disease

Risk factors for macrovascular cerebrovascular disease are multiple and can be additive. These risk factors include increasing age, hypertension (Amenta et al. 2002), cigarette smoking, hyperlipidemia, diabetes (Allen et al. 2004), atrial fibrillation, and hyperhomocysteinemia. Other risk factors include decreased physical activity, obesity, use of oral contraceptives, increased plasma fibrinogen, and a hypercoagulable state (activated protein C or S deficiency, antiphospholipid antibodies) (Giles and Rothwell 2006; Kakafika et al. 2007; Muscal and Brey 2007; Sanossian and Ovbiagele 2006; Spence 2001).

Chronic atrial fibrillation, aneurysms of the left ventricle, and poor left ventricular contraction increase risk of stroke by promoting the formation of thrombi within the chambers of the heart (Murtagh and Smalling 2006). Large artery atherosclerotic disease within the carotids or vertebrobasilar systems or an embolic source from the aortic arch can cause macrovascular stroke. Occasionally, there are rarer sources of emboli, such as paradoxical (via a patent foramen ovale), atrial myxoma, or infective, from endocarditis.

Small Vessel or Penetrating Artery Disease

Small vessel disease results in arterial wall changes, expansion of the Virchow-Robin spaces, perivascular parenchymal rarefaction, and gliosis. In addition, it can cause discrete small deep infarcts (lacunes) due to occlusion of long-perforating arterial branches. These changes are most commonly due to chronic hypertension, with secondary hypertrophy of the media of the arteriolar wall and subsequent deposition of fibrinoid material within the vessel wall. With time, the vessel lumen becomes entirely occluded, resulting in a small infarct. A rarer source of this pathology is microscopic emboli from a central source, or small vessel arteritis. These lacunae are found more typically in the internal capsule, deep gray nuclei, and white matter.

Chronic altered blood flow within small intracranial vessels can lead to diffuse white matter damage, also termed leukoaraiosis. Leukoaraiosis greater than 25% is considered to be pathological (Ball 1989). Subcortical vascular dementia is a diffuse small vessel disease with minimal or absent infarction that has homogeneous pathological and clinical features.

Neurotransmitters

Cerebrospinal fluid and autopsy studies show neurotransmitter deficits in vascular dementia. The cholinergic

(Mesulam et al. 2003), serotonergic, and hypothalamic-pituitary-adrenocortical axes have been implicated (Gottfries et al. 1994). Other neurotransmitters, including dopamine, glutamate, and γ-aminobutyric acid (GABA), have shown some evidence of involvement, but further studies are required. Because of the high degree of mixed pathology, determining the contribution of vascular and Alzheimer pathology is difficulty.

Animal studies suggest that vascular disruption is associated with cholinergic denervation (Moser et al. 2006). There is also reinforcement with neurotransmitters having a known role in modulating cerebral blood flow. For this reason, cholinesterase inhibitors have been used with some reported success (Wilkinson et al. 2003). The changes in cholinergic markers are not as significant in vascular dementia as in Alzheimer disease (Jia et al. 2004); in vascular dementia, changes are found in cholinergic terminal markers but not in receptor numbers. These changes based on dementia type have been confirmed in a study of 42 autopsy cases, in which tissue from subjects with either Alzheimer disease or mixed dementia had greater cholinergic deficit than did tissue from subjects with vascular dementia (Perry et al. 2005). Trials demonstrating that partial *N*-methyl-D-aspartate (NMDA) channel blockade by memantine is efficacious (Orgogozo et al. 2002) further reinforce that neurotransmitters have a role in vascular cognitive disorder.

Overlap With Alzheimer Disease

The overlap of various dementia pathologies is a new area of research. Population-based studies using DSM-IV criteria have shown that mixed dementia and vascular dementia are equally common (Knopman et al. 2003). In addition to finding an overlap between Alzheimer dementia and vascular dementia, studies have found similar overlaps between dementia with Lewy bodies and vascular change (Barber et al. 1999), indicating that vascular pathology may affect outcome in many disorders with cognitive decline. The commonality of risk factors between Alzheimer disease and vascular disease could be due to the co-occurrence of two common conditions or could be the result of common etiological factors. The amyloid beta plaque protein of Alzheimer disease, which is known to deposit within the blood vessels of the aging brain, can produce an angiopathy characterized by microinfarcts and hemorrhages. Amyloid angiopathy is present in more than half of Alzheimer disease patients and is almost universal in those with Down syndrome (Vinters 1987). The amyloid beta molecule could also have vasogenic actions through reactive oxygen species (Niwa et al. 2001). In fact, a number of provocative articles have suggested that vascular etiology underlies Alzheimer disease (de la Torre 2002).

Complex interactions between vascular pathology and Alzheimer pathology have been suggested. For example, amyloid angiopathy may enhance the formation of and/or compromise elimination of amyloid beta and phosphorylated tau, thus resulting in their accumulation (Nicoll et al. 2004). Cells with inadequate blood supply may themselves be predisposed to create these protein byproducts. Rat studies, in which researchers examined the expression of enzymes fundamental in pathways to create phosphorylated tau and amyloid beta, revealed that induced ischemia to brain cells increases the expression of these substances (Wen et al. 2004).

Whether or not vascular dementia and Alzheimer disease share common etiologies, research indicates that lacunar infarcts in the basal ganglia, thalamus, and deep white matter appear to greatly increase the risk for symptomatic Alzheimer disease (Snowdon et al. 1997). Also, the presence of frank strokes has been reported to double the rate of progression of dementia in Alzheimer disease (Heyman et al. 1998; Snowdon et al. 1997).

Assessment

History and Clinical Examination

A vascular etiology is suggested when dementia is accompanied by cerebrovascular risk factors and focal neurological findings. History taking should therefore include family history and personal history of hypertension, smoking, lipid profile, diabetes, arrhythmias, and evidence of other vascular pathologies such as cardiovascular and peripheral vascular disease. The classic stepwise progression of changes is characteristic of multi-infarct dementia. Specific characteristics in the history are associated with certain vascular cognitive disorders. For example, Binswanger disease typically has an onset in the fourth to seventh decades of life, and most patients with this disease have coexistent hypertension. Progression usually is slow, over a period of years, and includes deficits in cognition, changes in mood and behavior, and motor dysfunction. Early features are often mood and behavioral changes and early-onset urinary incontinence and gait abnormalities (Binswanger 1884). CADASIL, described earlier, affects persons in the third and fourth decades of life. These patients are less likely to have hypertension and are likely to have severe cerebrovascular disease.

A variety of scales are available for clinical use to determine the degree of an individual's cognitive impair-

ment. The most commonly used scale, the Mini-Mental State Examination (Folstein et al. 1975), is a poor choice for diagnosing vascular cognitive impairment (Black et al. 2007). Improvement in the bedside tools for assessment of cognition is under way. Assessment of mood using a scale such as the Geriatric Depression Scale (Jongenelis et al. 2007) is also important.

All patients with dementia should undergo routine laboratory testing as indicated in Chapter 4, "Medical Evaluation and Diagnosis." In some situations, echocardiography, Holter monitoring, and carotid duplex scanning may be indicated.

Neuroimaging

The use of neuroimaging is discussed extensively in Chapter 6, "Neuroimaging." Advances in neuroimaging have revolutionized the capacity to examine a patient for patterns of cerebral damage relevant to vascular-type cognitive disorders; the use of MRI to describe both severity and location of disease is a cornerstone of the NINDS-AIREN criteria. With the increased use of computed tomography (CT) and MRI, the number of patients being found to have "silent" vascular brain injury has increased.

Large epidemiological imaging studies have shown that one-third of older individuals had evidence of lacunar strokes (Longstreth et al. 1998). Although these strokes predispose individuals to further strokes (Longstreth et al. 2001), the association between the strokes and cognitive changes is not proven. No clear relationship has been shown between vascular lesion load and the presence of dementia (Ballard et al. 2004), and epidemiological imaging studies have shown that "silent" lesions are a common finding in healthy individuals (Longstreth et al. 2001).

Functional imaging techniques such as positron emission tomography (PET) (Kerrouche et al. 2006) and single photon emission computed tomography (SPECT) also have utility in differentiating vascular-type dementia from Alzheimer-type dementia. SPECT shows a pattern of multiple asymmetric perfusion deficits in multi-infarct dementia. PET shows that in subcortical vascular dementia, oxygen extraction fraction is maintained despite reduced perfusion. In contrast, Alzheimer disease is characterized by bilateral temporoparietal hypoperfusion on SPECT and hypometabolism on PET.

Neuropsychological Assessment

Neuropsychological testing is an essential part of the clinical assessment of patients with cognitive decline (see Chapter 5, "Neuropsychological Assessment in Dementia"). To distinguish vascular-type dementia from Alzheimer-type dementia, the clinician looks for characteristic changes in cognitive domains. Specifically, changes in attention, speed of information processing, and executive functioning are characteristic of vascular cognitive disorder. Given the nature of vascular disease, patients with vascular cognitive disorder can have patchy neuropsychological deficits. They tend to have better recall than patients with Alzheimer disease but to have poor verbal fluency and often more perseverative behavior. Neuropsychological findings vary depending on the site and extent of vascular damage; for example, deep white matter disease is reflected by reduced speed of processing and impaired dexterity and executive function.

Association With Psychiatric Disorders

The behavioral and psychiatric symptoms of dementia are addressed in Chapter 15, "Psychiatric Disorders in People With Dementia," and their management in Chapter 16, "Pharmacological Treatment of Neuropsychiatric Symptoms." The association between depression and vascular cognitive disorder led to introduction of the term *vascular depression* (Alexopoulos 1996). Evidence indicates that the severity of depression in vascular cognitive disorder relates to the severity of frontal lobe damage (Alexopoulos 2003; Naarding et al. 2007). Examination of patients with known vascular dementia revealed that over 70% had clinically significant anxiety and 20% had evidence of depression on standardized validated measures (Ballard et al. 2000). Although psychological symptoms are common in dementias of all types, both anxiety and depression were statistically more likely in those with vascular dementia than in those with Alzheimer-type dementia. Furthermore, the presence of depression may have important prognostic implications; Ballard et al. (2000) found evidence that vascular depression may be an early indicator of later development of vascular cognitive disorder.

Treatment

Epidemiological data suggest that stroke prevention prevents vascular dementia (Goldstein 2006). Therefore, addressing all the risk factors of stroke and the use of treatments to prevent cerebrovascular disease is encouraged. However, the effects of these therapies on the outcome of small vessel and deep white matter ischemia have not been well studied. Cardiovascular risk factors should be treated not only to delay progression of cognitive impairment but also to prevent the development of vascular co-

morbidity. Thus, medication and lifestyle interventions to treat hypertension, hyperlipidemia, and diabetes are important. Patients should be encouraged to eat a low-fat diet and to take appropriate levels of folate and B vitamins. Increased homocysteine levels, which are a key risk factor for stroke, are associated with low levels of folate and B vitamins (Smith 2006). Antiplatelet agents, anticoagulants, endarterectomy, and stenting all have their place in the management of vascular disorders.

Neuroprotective Agents

Neuroprotective drugs have been investigated in treatment of cerebrovascular disease. Nimodipine, propentofylline, and posatirelin are currently in clinical trials for vascular dementia (Martinez-Vila et al. 2006).

Neurotransmitter Modulators

Cholinesterase inhibitors and NMDA receptor antagonists have shown promise as treatments for patients with vascular dementia and vascular cognitive impairment. The cholinesterase inhibitors donepezil and galantamine have had modest positive results in controlled trials (Black et al. 2003; Erkinjuntti et al. 2002). In two controlled trials, the NMDA receptor antagonist memantine has been shown to have a small beneficial effect on cognition but no improvement on global measures of function (McShane et al. 2006; Orgogozo et al. 2002; Wilcock et al. 2002). Further study is awaited to permit approval of these medications for the treatment of vascular cognitive disorder.

Supportive Treatments

Essential supports for patients and their caregivers include appropriate referral to community services, addressing caregiver stress, and addressing the legal and ethical issues of cognitive decline. Treatment of mood disorders and challenging behaviors is equally important, both in terms of patient quality of life and the ability of caregivers to continue their role.

Outcome

Compared with persons with Alzheimer disease, persons with vascular cognitive disorder have a shorter life expectancy (Chui and Gonthier 1999), probably due to the underlying vascular disorder and comorbidities. In patients with vascular dementia, no relationship has been found between cognitive progression and rate of atrophy detected by neuroimaging (O'Brien et al. 2001). The Canadian Study of Health and Aging found that 2.6% of participants had vascular cognitive impairment and 1.5% met criteria for vascular dementia. At 5-year follow-up of patients with vascular cognitive impairment without dementia, all those who were still alive had progressed to a diagnosis of dementia (Wentzel et al. 2001). Prospective studies have confirmed this high rate of conversion from vascular cognitive impairment to dementia (Meyer et al. 2002). For this reason, targeting of this group for preventive treatment is important.

Conclusion

As the population ages, the incidence of vascular disease will increase, and therefore the contribution of vascular change to cognitive decline, whether alone or in combination with Alzheimer disease, will rise. Recent research on vascular disease is promising new options for treatment. In trials on the effects of cholinesterase inhibitors on vascular dementia, benefits have been modest, and clinical applications are not yet delineated clearly; however, the research has been limited by the inclusion of only subjects with late-stage disease and with entry criteria requiring significant memory impairment (Parnetti et al. 2007). New work with treatments in earlier vascular cognitive impairment with clear diagnostic criteria, in addition to primary and secondary prevention with optimization of cardiovascular risk, holds promise for reducing the burden of disease within the community.

KEY POINTS

- Diagnostic criteria for vascular cognitive disorder need to be refined.
- Significant overlap exists between vascular cognitive disorder and Alzheimer disease and possibly other dementias.
- Vascular dementia has a poor prognosis if untreated.

- Identification and treatment of vascular risk factors is essential.
- Psychological comorbidity with vascular dementia is common and should be detected and treated.

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CHAPTER 11

Dementia With Lewy Bodies and Other Synucleinopathies

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The synucleinopathies are a group of neurodegenerative disorders that share the common pathology of fibrillar aggregates of α-synuclein protein in selective populations of neurons and glia. The most common of these disorders are dementia with Lewy bodies, Parkinson disease, multiple systems atrophy, and pure autonomic failure. The underlying pathological lesion in these disorders is the intracellular aggregation of α-synuclein. However, α-synuclein pathology is also present in many other neurodegenerative diseases such as Alzheimer disease and Down syndrome (Table 11–1). Synucleinopathies are characterized by variable degrees of progressive decline in cognitive, motor, behavioral, and autonomic function. The Lewy Body Dementia Association (http://www.lewybodydementia.org) estimates that 1.5 million Americans are affected by illnesses with clinical features, including dementia, extrapyramidal signs, hallucinations, fluctuating cognition, sensitivity to neuroleptic medications, and rapid eye movement (REM) behavioral disorder (RBD). Parkinson disease with dementia and diffuse Lewy body disease are also designated as Lewy body disorders (Lippa et al. 2007).

The Synucleins

The synucleins are a family of small, soluble proteins predominantly expressed in neurons. α-Synuclein is expressed ubiquitously in neurons (George et al. 1995; Jakes et al.

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1994). β-Synuclein was identified in bovine brain (Tobe et al. 1992), and γ-synuclein was identified in metastatic breast cancer tissue (Ji et al. 1997). The synuclein proteins range from 123–143 amino acid residues. They have unique structural properties and a significant degree of homology as a group (Lavedan et al. 1998). Whereas α- and β-synuclein are localized primarily in presynaptic terminals in proximity to synaptic vesicles (Nakajo et al. 1994), γ-synuclein is distributed diffusely through the cytosol of neurons and may have a role in cytoskeletal maintenance (Buchman et al. 1998) or as a centrosome protein (Surguchov et al. 2001). Neither β- nor γ-synuclein has been associated with neurodegenerative disease. The genes for α-, β-, and γ-synuclein have been mapped to chromosomes 4q21.3–q22, 5q35 (Spillantini et al. 1995), and 10q23.2–q23.3 (Lavedan et al. 1998; Ninkina et al. 1998), respectively.

Aggregates of α-synuclein are present in neurons as Lewy bodies and dystrophic Lewy neurons, or as cytoplasmic inclusions in oligodendrocytes. The distribution of synuclein-related pathology is highly variable among these disorders, which may account for the relative differences in clinical presentation. For example, Lewy bodies predominate in the neocortex in diffuse Lewy body disease, the substantia nigra in Parkinson disease, and cerebellar and brainstem tubulofilamentous inclusions are seen in multisystems atrophy.

The presence of α-synuclein in neurodegenerative disorders was recognized shortly after the identification of a missense mutation (A53T) in the α-synuclein gene of Mediterranean and Greek families with early-onset Parkinson disease (Krüger et al. 1998; Polymeropoulos et al. 1997).

The functional role of α-synuclein is unknown. Its primary structure has three distinct regions: the N-terminal region (residues 1–60), the central region (residues 61–95), and the C-terminal region (residues 96–140). The central region contains a highly aggregation-prone sequence, and the C-terminal region is highly enriched in acidic residues (Han et al. 1995). The N terminus has seven repetitions of a degenerate 11-residue motif XKTKEGVXXXA (where X is any amino acid), causing a repetitive variation in hydrophobicity. The presence of this protein in a highly unfolded state allows it to undergo a large number of distinct conformational changes; α-synuclein can interact stably with phospholipid vesicles containing negatively charged head groups (Ramakrishnan et al. 2003), phospholipid membranes, fatty acids, and lipids (Cole et al. 2002). This close association of synuclein with lipid membranes suggests a role in the regulation of vesicular release (Bonini and Giasson 2005) and/or turnover (Sharon et al. 2003) , membrane fluidity, fatty acid uptake and metabolism, lipid packing, and the release of neurotransmitters (Paleologou et al. 2005). Developmental studies in animals suggest that its expression in certain neurons is associated with the acquisition of learning (George et al. 1995), and it is thought to play a role in synaptic plasticity (Murphy et al. 2000). A neuroprotective role for α-synuclein is suggested by its interactions with cysteine-string protein-α, a synaptic vesicle protein that is essential for neuronal survival (Chandra et al. 2005).

TABLE 11–1. Disorders with synuclein pathology

Dementia with Lewy bodies
Parkinson disease
Sporadic
Familial (with mutations other than the Parkinson gene)
Alzheimer disease
Sporadic
Familial forms (amyloid precursor protein, presenilin , and presenilin 2 mutations)
Down syndrome
Multiple system atrophy
Shy-Drager syndrome
Olivopontocerebellar atrophy
Striatonigral degeneration
Pure autonomic failure
Neurodegeneration with brain iron accumulation
Type 1 (formerly Hallervorden-Spatz)
Type 2 (Neuroaxonal dystrophy)
Other disorders where synuclein inclusions have been described
Amyotrophic lateral sclerosis
Pick disease
Creutzfeldt-Jacob disease
Traumatic brain injury

Dementia With Lewy Bodies

Since the late 1980s, dementia with Lewy bodies has become increasingly recognized as an important cause of cognitive decline in older adults. The term *dementia with Lewy bodies* was established by the Dementia with Lewy Bodies Consensus Conference (McKeith et al. 1992b). It is probably the second most common cause of neurodegenerative dementia after Alzheimer disease; neocortical Lewy bodies are found in up to 40% of brains of all elderly patients with dementia (Galasko et al. 1994).

Epidemiology

The prevalence of dementia with Lewy bodies has been difficult to establish. A community study of elderly individuals older than age 65 years in the United Kingdom found that it accounted for 11% of those with dementia (Stevens et al. 2002), whereas a Finnish study of a population of age 75 years and older reported a prevalence of 5%, dementia with Lewy bodies accounting for 22% of all demented subjects (Rahkonen et al. 2003). From postmortem studies, up to 40% of autopsied demented patients have sufficient cortical Lewy bodies to be diagnosed as dementia with Lewy bodies (Barker et al. 2002; Galvin et al. 2006), suggesting that the antemortem diagnosis of dementia with Lewy bodies is often missed.

Clinical Features and Diagnostic Criteria

The consensus criteria for diagnosing dementia with Lewy bodies require progressive cognitive decline severe enough to cause functional or occupational impairment (e.g., dementia) as a central feature for diagnosis (McKeith et al. 2005). Unlike Alzheimer disease, prominent memory deficits may not occur early in the disease but are usually evident with disease progression. Early in the course of dementia with Lewy bodies, deficits on tests of attention, executive function, and visuospatial ability may be especially prominent. In addition to dementia, there should be at least two of three core features for a diagnosis of probable dementia with Lewy bodies: fluctuating cognition, recurrent well-formed visual hallucinations, and spontaneous parkinsonism. At least one core feature is required for a diagnosis of possible dementia with Lewy bodies. Suggestive features include REM sleep behavior disorder, severe neuroleptic sensitivity, and low dopamine transporter uptake in the basal ganglia demonstrated by single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging. In the absence of two core features, the diagnosis of probable dementia with Lewy bodies can be made if at least one suggestive feature is also present. The diagnosis of probable dementia with Lewy bodies cannot be made on the basis of suggestive features alone (McKeith et al. 2005).

Supportive features for the diagnosis of dementia with Lewy bodies include repeated falls, syncope, transient loss of consciousness, severe autonomic dysfunction, depression, systematized delusions, or hallucinations in other modalities. Although these features may support the clinical diagnosis, they lack diagnostic specificity.

These criteria have 83% sensitivity and 95% specificity for the presence of cortical Lewy bodies (McKeith et al. 2000a). However, their diagnostic utility is limited. They appear to be more predictive of cases with pure Lewy body pathology and do not reliably differentiate pure dementia with Lewy bodies (which is uncommon) from the frequent mixture of Lewy bodies with Alzheimer pathology.

Currently there are no radiological or biological markers that aid reliably in the diagnosis of dementia with Lewy bodies, and current therapies are limited to drugs that provide symptomatic control of the cognitive and behavioral pathology. Despite these limitations, early detection has therapeutic implications. For example, these patients appear to have better responses to cholinesterase inhibitors than Alzheimer disease patients (Liberini et al. 1996). Physicians also need to avoid using classic neuroleptics for psychotic symptoms in these patients because they are very sensitive to neuroleptics, even at very low doses. Up to 57% of dementia with Lewy bodies patients may develop exaggerated extrapyramidal signs, sedation, immobility, or neuroleptic malignant syndrome (McKeith et al. 1992a). Early diagnosis also will allow families to take measures to enhance the safety of the environment as a result of patients' tendency to recurrent falls.

Cognitive Profile

Dementia with Lewy bodies is insidious in onset, with gradual progression. Whereas Alzheimer disease is characterized by a cortical pattern of deficits, dementia with Lewy bodies predominantly involves frontal subcortical structures early on. The frontal subcortical deficits mediate executive and visusospatial functions in association with rapidly fluctuating attentional deficits and memory loss (Salmon et al. 1996). As the disease progresses, temporoparietal cortical deficits such as aphasia, apraxia, and spatial disorientation also can be seen.

The differences in cognitive profile between dementia with Lewy bodies and Alzheimer disease are partially quantitative, and overlap increases with disease progression. Alzheimer disease patients may demonstrate extrapyramidal symptoms, hallucinations, and attention deficits, and dementia with Lewy bodies patients may have significantly impaired memory and few perceptual disturbances at different points in their disease. Given that approximately 30% of dementia with Lewy bodies patients have a cortical pattern of dementia almost indistinguishable from Alzheimer disease, and that 90% of dementia with Lewy bodies patients have concomitant Alzheimer disease pathology, it is not surprising that many dementia with Lewy bodies patients are misdiagnosed as having Alzheimer disease (Lippa et al. 1994).

Impairment in basic attention, visual perception, visual construction, and memory distinguish dementia with Lewy

TABLE 11–2. Patterns of cognitive impairment between dementias

Disorder	Learning and memory	Attention and concentration	Executive functioning	Language functioning	Visuospatial functioning
Alzheimer disease	+++	+ to +++	+ to +++	+ to +++	+ to +++
Parkinson disease	0 to +	0 to ++	0 to ++	0	0
Parkinson disease with dementia	0 to +++	++ to +++	++ to +++	0 to ++	+ to +++
Dementia with Lewy bodies	0 to +++	++ to +++	++ to +++	0 to ++	+ to +++

Note. 0=no impairment; +=mild impairment; ++=moderate impairment; +++=severe impairment.

bodies from normal aging, with a sensitivity of 88.6% and specificity of 96.1% (Ferman et al. 2006). In the next section, we describe the pattern of deficits seen with dementia with Lewy bodies in specific cognitive domains (Table 11–2).

Executive and Attentional Dysfunction

The attentional and executive dysfunction of persons having dementia with Lewy bodies could result from combined cortical and nigrostriatal pathology; they often exhibit executive dysfunction in the form of impaired judgment, organization, and planning. Neuropsychological testing can detect these executive deficits even at an early stage with instruments such as the Wisconsin Card Sorting Test, the Trail Making Test, and the Stroop Test (see Chapter 5 of this volume, "Neuropsychological Assessment in Dementia").

Attentional dysfunction is a prominent feature of dementia with Lewy bodies. This ranges from simple processing to selective attention, divided attention, and supervisory attentional control. Performance is further compromised in high-demanding tasks and in tasks with an executive or spatial component (Bradshaw et al. 2006). Examples of attentional tasks include the digit span, computer-based measures of simple and choice reaction time, and digit vigilance.

Executive demands seem to affect attentional variability, and there is more performance variability in tasks that require more active recruitment of executive control processes, because executive control is needed to maintain a goal-directed course of attention and to minimize lapses of attention or transient fluctuations in performance.

Visuospatial

A consistent feature of dementia with Lewy bodies is marked impairment in visuospatial and visuoperceptual function. These patients often have difficulty navigating in their homes or even moving out of a bed or chair. Although impairment in visual tasks might be negatively affected by perceptual and executive difficulties, it is often present in basic visual tasks that do not require an executive function (Mori et al. 2000).

Dementia with Lewy bodies patients may exhibit differential involvement of visual tasks with more impairment in visual perceptual processing than visual spatial processing (Mosimann et al. 2004), perhaps because of involvement of the cortical association areas (Shimizu et al. 2005).

Brief cognitive screening tests may miss deficits in visuospatial or constructive abilities at the very mildest stage. Visuospatial dysfunction can be more readily detected by formal psychometric testing, with the Block Design subtest of the Wechsler Adult Intelligence Scale or with figure copying (Wechsler 1991). Approximately 80% of dementia with Lewy bodies patients perform poorly on the Block Design subtest, even with mild impairment (Salmon et al. 1996). Visuospatial and constructional deficits may serve as an important clue to Lewy body pathology in early stages, including mixed Alzheimer and Lewy body pathology.

Memory

Patients with pure Lewy body pathology have relative preservation of memory in the early stages compared with Alzheimer disease (McKeith et al. 1992b). Memory impairment develops with disease progression, but the memory impairment in dementia with Lewy bodies predominantly reflects deficits in retrieval, whereas the primary substrate of memory impairment in Alzheimer disease is impaired encoding (Burn 2006).

These patients have poor initial learning and retrieval with mild deficits in consolidation or forgetting over a delay. Relative preservation of verbal skills is an important feature of pure Lewy body pathology, and dementia with

Lewy bodies patients show no impairment or only mild impairment in measures of verbal memory and confrontation naming (Johnson et al. 2005).

The performance of patients with combined Alzheimer and Lewy body pathology is similar to Alzheimer disease patients on the subsets of verbal memory, indicating that the additional Lewy body burden does not negatively affect verbal performance in Alzheimer disease patients. This is in contrast to visuosospatial dysfunction, in which the combined pathology has an additive effect (Johnson et al. 2005).

Language

Dementia with Lewy bodies patients have more severe impairment than Alzheimer patients in verbal fluency. In Alzheimer disease, there is more severe impairment in category fluency than letter fluency. Both appear to be affected to the same degree in dementia with Lewy bodies. In addition, Lewy body patients may exhibit mild confrontation-naming deficits.

Psychiatric Features

Visual hallucinations are frequently present early and occur intermittently throughout the course of illness. The visual hallucinations consist of fully formed, detailed, colored three-dimensional objects, persons, or animals (McKeith et al. 1994). The emotional response to hallucinations varies from indifference to excitement or fear, and there may be some insight into their unreality. Hallucinations occur in other modalities, including auditory, tactile, and olfactory. Auditory hallucinations occur in 13%–30% of patients at presentation and 13%–45% at any point in their illness (McKeith 2000), but auditory hallucinations rarely occur in the absence of visual hallucinations.

Visual hallucinations occur in 59%–85% of autopsy-confirmed dementia with Lewy bodies cases and in 11%–28% of autopsy-confirmed Alzheimer disease patients (Harding et al. 2002; Klatka et al. 1996). The occurrence of visual hallucinations in the first 4 years after dementia onset has a positive and negative predictive value for dementia with Lewy bodies of 81% and 79%, respectively (Ferman et al. 2003).

There is a strong association between visual hallucinations and cholinergic depletion in the temporal cortex and the basal forebrain (Harding et al. 2002). The hallucinations of dementia with Lewy bodies do not seem to correlate with the dose of levodopa (L-dopa) or the occurrence of motor fluctuations seen with dopaminergic therapy (Sanchez-Ramos et al. 1996). Other suggested mechanisms for visual hallucinations include dysregulation of REM sleep with the intrusion of dreams into wakefulness (Boeve et al. 2003b).

Other psychiatric features in dementia with Lewy bodies include delusions in 56% of patients at first presentation and 65% at some point in their illness. In contrast to the vague persecutory delusions often seen in Alzheimer disease that are based mostly on confabulation and memory loss, delusions in dementia with Lewy bodies tend to be fixed and complex and represent recollections of hallucinations and perceptual disturbances (McKeith 2000).

A history of intercurrent depression has been reported in 58% of persons with Parkinson disease dementia, 50% in dementia with Lewy bodies, and 14% in Alzheimer disease cases coming to autopsy (Klatka et al. 1996). Other psychiatric features include apathy, anxiety, illusions, Capgras syndrome, and reduplicative paramnesia.

Motor Features

Spontaneous parkinsonism is one of the core features of dementia with Lewy bodies (Table 11–3). The distinction between dementia with Lewy bodies and Parkinson disease with dementia is based on the temporal relationship of dementia onset to motor impairment; in dementia with Lewy bodies, cognitive impairment precedes motor impairment by more than 12 months. The reverse is true for Parkinson disease with dementia (McKeith et al. 1996). The onset and severity of parkinsonism in dementia with Lewy bodies are highly variable.

Many Lewy body patients develop a symmetric akinetic-rigid syndrome. Tremor is less common than bradykinesia, facial masking, and rigidity, and tends to be maximal with posture/action rather than at rest. Myoclonus is seen in 18.5% of Lewy body patients and rarely seen in nondemented Parkinson disease patients (Louis et al. 1997).

Postural instability and gait difficulty are more prominent features of dementia with Lewy bodies and Parkinson disease with dementia than uncomplicated Parkinson disease. This may indicate more involvement of nondopaminergic pathways in dementia with Lewy bodies and Parkinson disease with dementia than pure Parkinson disease. Motor features of dementia with Lewy bodies are less responsive to dopaminergic treatment than in Parkinson disease, but a beneficial response has been seen in some patients in a few small trials (Molloy et al. 2005).

Cognitive Fluctuations

Fluctuations in cognition are seen in 15%–80% of cases of dementia with Lewy bodies and are one of the hallmarks of this disease (Ballard et al. 2002a). These often involve waxing and waning of cognition, functional abilities, or arousal in the absence of a clear precipitant. They are often described as episodes of behavioral confusion, inattention, hypersomnolence, and incoherent speech alternating with

TABLE 11–3. Comparison of extrapyramidal features in dementias

Disorder	Specific parkinsonian findings
Alzheimer disease	Parkinsonism tends to be later in course; rigidity, bradykinesia, tremor (resting or postural) most obvious
Parkinson disease	Masked facies, stooped posture, reduced arm swing. Unilateral or asymmetric rigidity, bradykinesia, resting tremor, and postural instability; signs clearly are levodopa (L-dopa) responsive
Parkinson disease with dementia	Same as in Parkinson disease, but over time, bilateral involvement, marked postural instability, and loss of L-dopa responsiveness
Dementia with Lewy bodies	Masked facies, stooped posture, reduced arm swing similar to Parkinson disease and Parkinson disease with dementia, but tremor is less asymmetric and more postural than at rest
Multisystems atrophy	Rigidity less asymmetric and minimally L-dopa responsive in the striatonigral variant; ataxia and spasticity prominent in the olivopontocerebellar atrophy variant; orthostatic hypotension prominent in the Shy-Drager syndrome variant

episodes of lucidity and capable task performance. Patients may be described as staring into space or as dazed. These episodes can last minutes to days and can vary from alertness to stupor. Transient episodes of disturbed consciousness in which patients are found mute and unresponsive for a few minutes may represent one extreme form of fluctuations.

Because of the variability in the description and quantifications of fluctuations in Lewy body patients, several scales have been developed, including the Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale, and the Mayo Fluctuations Questionnaire (Ferman et al. 2004). The Mayo scale describes four features of fluctuations that can reliably distinguish dementia with Lewy bodies from Alzheimer disease or normal aging (Table 11–4): 1) daytime drowsiness and lethargy, 2) daytime sleep of 2 or more hours, 3) staring into space for long periods, and 4) times when a patient's flow of ideas seems disorganized, unclear, or not logical. Three or four features of this composite occurred in 63% of patients who had dementia with Lewy bodies compared with 12% of those who had Alzheimer disease and 0.5% of normally functioning elderly. The presence of three or four of these features yielded a positive predictive value of 83% for the clinical diagnosis of dementia with Lewy bodies against an alternate diagnosis of Alzheimer disease.

Excessive Daytime Drowsiness

Dementia with Lewy bodies patients often experience daytime drowsiness or somnolence. It is important to rule out secondary causes of daytime sleepiness, including medications and primary sleep disorders such as sleep apnea. Approximately three-quarters of patients have a significant number of arousals not accounted for by medication, periodic limb movements of sleep, or sleep apnea (Boeve et al. 2003a).

Rapid Eye Movement Sleep Behavior Disorder

RBD is characterized by loss of normal muscle atonia during REM sleep associated with excessive activity while dreaming. Increased muscle activity during REM sleep occurs along with dream content and can range from elevated muscle tone to complex behavioral sequences, such as acting out dreams.

RBD is associated with a group of synucleinopathies, including dementia with Lewy bodies, Parkinson disease, and multiple systems atrophy, and may precede the diagnosis by years, but it rarely occurs in tau-predominant neurodegenerative conditions such as Alzheimer disease (Boeve et al. 2001). This relationship with synucleinopathies has been supported by neuropathological confirmation of Lewy bodies in patients with RBD and no clinical evidence of dementia or psychosis (Galvin et al. 2001). The presumed pathophysiological mechanism of RBD involves damage to the descending pontine-medullary reticular formation (including the magnocellular reticular formation) or sublaterodorsal nucleus that leads to a loss of the normal REM sleep inhibition of the spinal alpha-motor neurons.

Autonomic Dysfunction

Autonomic dysfunction is a common clinical sign in dementia with Lewy bodies and is a feature shared by most of the other synucleinopathies (McKeith et al. 2005). Autonomic dysfunction is not included in the consensus criteria, but some of the supportive features such as recur-

TABLE 11–4. Commonly used fluctuation scales

Scale	Items	Advantages	Limitations
Clinician Assessment of Fluctuation[a]	Frequency of fluctuating confusion 1=1 per month 2=monthly-weekly 3=weekly-daily 4=≥daily Duration of fluctuating confusion 0=seconds 1=≤5 minutes 2=5–60 minutes 3=≥1 hour 4=≥1 day	Sensitivity=83% Specificity=90%	High reliance on clinical expertise Not standardized; does not provide a clear definition of "confusion" Interrater reliability not established
One Day Fluctuation Assessment Scale[a]	Seven items on the day before the assessment: Falls Fluctuations Drowsiness Attention Disorganized thinking Altered consciousness Communication	Sensitivity ≥80% Good correlation with variability on a computer reaction time task of vigilance Good discrimination between Alzheimer disease and dementia with Lewy bodies	Interrater reliability not established
Mayo Fluctuations Questionnaire[b]	Four items assessed: Daytime drowsiness and lethargy Daytime sleep of 2 hours or more Staring into space for long periods Times when a patient's flow of ideas seems disorganized, unclear, or not logical	Allows discrimination between dementia with Lewy bodies and Alzheimer disease	Needs validation in an autopsy confirmed dementia with Lewy bodies population

[a]Walker et al. 1999.
[b]Ferman et al. 2004.

rent falls and transient loss of consciousness might be explained by underlying autonomic dysfunction. Although these autonomic features tend to occur late, there have been cases with early and prominent involvement. There is also evidence of involvement of the peripheral nervous system with numerous Lewy bodies in the sympathetic neurons and autonomic ganglia, and to a lesser extent in the intermediolateral cell column.

The most serious manifestation of autonomic dysfunction is orthostasis, which is symptomatic in approximately 15% of patients. Other features include decreased sweating, sialorrhea, seborrhea, heat intolerance, urinary dysfunction, constipation or diarrhea, and erectile dysfunction. These patients have a higher frequency of carotid hypersensitivity than normal elderly patients or patients with Alzheimer disease (Kenny et al. 2002, 2004).

Neuroleptic Sensitivity

Even very low doses of neuroleptics can produce significant side effects. Approximately 57% of dementia with Lewy bodies patients, 39% of patients with Parkinson disease with dementia, and 27% of patients with Parkinson disease develop severe neuroleptic sensitivity (Aarsland et al. 2005). It is not possible to predict the occurrence of these adverse motor reactions, but they are generally more common with the neuroleptics that are potent dopamine-2 (D_2) receptor antagonists.

Differential Diagnosis

Both baseline and longitudinal differences in cognitive, psychiatric, and functional deficits have been observed between dementia with Lewy bodies and Alzheimer disease (Table 11–2). Men are more likely to have dementia with Lewy bodies; Alzheimer disease has a female predominance. Persons with Lewy bodies are also more likely to exhibit psychiatric symptoms and have greater functional impairment at the time of diagnosis. Recent reports have addressed the role of domain-specific neuropsychological testing in distinguishing between dementia with Lewy bodies and Alzheimer disease (Rippon and Marder 2005). The diffuse cortical and subcortical Lewy body pathology produces cognitive impairment with predominant visuospatial and psychomotor deficits (Stern et al. 1993).

In general, memory loss and naming is less impaired in patients with dementia with Lewy bodies than patients with Alzheimer disease. The performance of Lewy body patients on memory tests lies midway between that of Alzheimer disease patients, who have more impairment (Helkala et al. 1988), and those of other subcortical dementias such as progressive supranuclear palsy.

Lewy body patients have less impairment in retention than Alzheimer disease patients, with more benefit from retrieval cues and less propensity to produce intrusion errors (Salmon et al. 1996). Recognition memory remains fairly stable in dementia with Lewy bodies and may be its only significant difference from Alzheimer disease in cognitive performance over time.

The more prominent involvement of executive functions in dementia with Lewy bodies may correlate with the presence of Lewy bodies in the frontal, cingulated, and inferior temporal cortex as well as more severe cholinergic depletion in the temporal, parietal, and midfrontal areas.

In summary, dementia with Lewy bodies patients have more neuropsychiatric features, more intense fluctuations, and are relatively more impaired in attention, executive functions, and visual constructional skills than patients with Alzheimer disease. Impairment in visuoperceptual tasks and attentional executive impairment has been shown to strongly and consistently distinguish Lewy body patients from normally functioning elderly or Alzheimer patients (Collerton et al. 2003).

Parkinson Disease With Dementia

The initial descriptions of Parkinson disease did not include cognitive problems as an important clinical feature. More recently, clinicians have come to realize that cognitive impairment occurs often and is among the most debilitating symptoms associated with disease progression. It is estimated that up to 14% per year of Parkinson disease patients who are over age 70 years will develop at least mild dementia (Aarsland et al. 2001a, 2003; Galvin 2006).

DSM-IV-TR defines Parkinson disease dementia as cognitive and motor slowing, executive dysfunction, and impaired memory retrieval (American Psychiatric Association 2000). However, there are no operationalized criteria to characterize Parkinson disease with dementia or define the clinical boundaries between pure Parkinson disease and Parkinson disease with dementia. No major differences have been found in the two entities (dementia with Lewy bodies and Parkinson disease dementia). They differ only in whether the cognitive impairment precedes or follows the motor signs by 12 months (McKeith et al. 2005).

Dementia with Lewy bodies and Parkinson disease with dementia both may have psychiatric symptoms, autonomic symptoms, RBD, cognitive fluctuations, and neuroleptic sensitivity. The neuropsychological profiles in Parkinson disease with dementia and dementia with Lewy bodies are similar, with prominent deficits in attention, executive dysfunction, visuospatial function, language function, memory retrieval, and behavior.

Epidemiology

Parkinson disease affects 1 in 100 individuals over age 60 years (Galvin et al. 2001) and 4%–5% of those over age 85 years (approximately 1.5 million Americans). Yearly incidence rates of Parkinson disease with dementia increase with age from 3% per year before age 65 years to 14% per year over age 70 years. The prevalence rates range widely from less than 10% to greater than 80% (Aarsland et al. 2001a, 2003; Hughes et al. 2000). The prevalence of Parkinson disease with dementia is approximately two to six times that of age-matched control subjects without Parkinson disease (Aarsland et al. 2003; Galvin 2006).

Risk Factors for Cognitive Decline in Parkinson Disease

Parkinson disease is often associated with cognitive decline. However, only a portion of patients with cognitive impairment develop dementia, and multiple attempts have been made to identify risk factors for progression to dementia. Visual hallucinations, typically of nonthreatening animals or people, were commonly reported in Parkinson disease even prior to the use of L-dopa (Fenelon et al. 2006) and are the strongest clinical predictor of dementia (Galvin et al. 2006). Age is another important risk factor (Levy et al. 2000). The

cumulative risk of dementia by age 85 years is over 65% (Marti et al. 2003). Advanced axial extrapyramidal involvement such as bradykinesia, rigidity, or postural instability also appears to increase the risk of dementia (Galvin et al. 2006) and the rate of cognitive decline once dementia develops. Among the motor predictors, bilateral onset of motor symptoms and declining response to L-dopa also appear to increase the risk of dementia (Padovani et al. 2006).

Cognitive Profile

The cognitive profile is similar to that of dementia with Lewy bodies and is characterized by relatively marked executive dysfunction resulting in errors in planning and sequencing, as well as marked impairment in attention, visuopatial, and constructional abilities (Lees and Smith 1983). Aside from verbal fluency, there is relative preservation of cortical functions such as language, limb praxis (Rippon et al. 2005), and perceptual processing in the early stages. Similar to dementia with Lewy bodies, memory impairment is less prominent than in Alzheimer disease, and there may be relative preservation of recall (Janvin et al. 2006).

Compared with nondemented Parkinson patients, those with dementia are more likely to have visual or auditory hallucinations, delusions, and depression. They also tend to have a higher frequency of aphasia and impairment in visuoconstructional tasks such as clock drawing. Other distinctive clinical features for Parkinson disease with dementia include sensitivity to neuroleptic medications, fluctuations in cognition, myoclonus, and sleep disturbances.

Executive Function

Patients who have Parkinson disease with dementia have impaired ability to plan, organize, and regulate goal-directed behavior. In contrast to patients with frontal cortical dysfunction, patients with Parkinson disease have difficulty with shifting attention to novel stimuli (Owen et al. 1993). These patients also have impaired attention comparable to that in dementia with Lewy bodies.

Visuospatial Abilities

Impairment in visuoperceptual and visuomotor abilities is seen in Parkinson disease with and without dementia (Stern et al. 1983). In the earliest stages of the disease, there is little impairment in visuospatial tasks such as constructional praxis, mental rotation, and set shifting.

Memory

The memory impairment in Parkinson disease with dementia is characterized by impaired semantic and episodic memory with reserved recognition memory and benefit from cuing. It is mostly associated with impaired registration or retrieval of information during the early retention phase of short-term memory (Burn 2006). Parkinson disease patients often exhibit impaired verbal and nonverbal short-term recall and recognition in tests of logical memory and associative learning (Sahakian et al. 1988). A similar pattern of performance has been shown on verbal and nonverbal recognition tasks.

Some studies suggest that Parkinson disease patients are impaired in long-term recall, although the relative rate of decline in long-term recall in relation to immediate recall is similar to that of normally functioning elderly subjects (Levin et al. 1989).

Language

Language processing and comprehension are relatively well preserved in Parkinson disease with dementia compared to Alzheimer disease, with the exception of verbal fluency, which is more compromised in the former. Parkinson disease with dementia patients have also been reported to have naming deficits and difficulties with sentence comprehension. Decreased content of spontaneous speech is also seen but to a lesser degree than in Alzheimer disease, and mild deficits on tests of semantic fluency have been reported (Monsch et al. 1992).

Parkinson disease with dementia patients exhibit motor speech abnormalities in the form of dysarthria, agraphia, decreased phrase length, and impaired speech melody. Many of the language deficits in patients in fact could be the result of executive dysfunction with inefficient internally generated search strategies.

Psychiatric Features

Neuropsychiatric features such as hallucinations, delusions, sexual disinhibition, and adverse reactions to antipsychotics are more common in dementia with Lewy bodies than in Parkinson disease. However, approximately 61% of Parkinson disease patients exhibit neuropsychiatric disturbances. The most common disturbances are depression (38%), hallucinations (27%), delusions (6%), anxiety (40%), sleep disturbances (60%–90%), and sexual misdemeanor (5%–10%).

The recurrent visual hallucinations are similar in both Parkinson disease with dementia and dementia with Lewy bodies, and are aggravated in both by dopaminergic treatment. The total prevalence of hallucinations in an outpatient sample of Parkinson disease patients, 63% of whom had evidence of cognitive impairment, was 9% although the study did not specify how many of these were drug related (Meco et al. 1990). Galvin et al. (2006) estimate that

visual hallucinations increase the risk of developing dementia 20-fold.

Cognitive impairment is the main risk factor for L-dopa-induced hallucinations in Parkinson disease patients (Fenelon et al. 2006). Other clinical correlates of psychosis in Parkinson disease are old age, advanced Parkinson disease, a history of depression, and coexistent sleep disorder, including altered dream phenomena and sleep fragmentation.

Depression

Estimates of the prevalence of depression in Parkinson disease range from 20%–70% (Sano et al. 1989). Risk factors for depression include early onset of Parkinson disease, presence of hallucinations or delusions, and an akinetic rigid presentation (as opposed to tremor predominant forms). The incidence of depression appears unrelated to the presence or absence of dementia or the severity of motor impairment (McKeith 2000). Anxiety co-occurs with depression in up to 40% of Parkinson disease patients (Henderson et al. 1992; Menza et al. 1993), and apathy is common with a frequency of 15% (Aarsland et al. 1999a).

It is important to recognize depression as a confounding factor in cognitive and motor impairment. Kuzis et al. (1997) found that depressed Parkinson disease patients performed worse on neuropsychological testing than physically healthy control subjects matched for depression severity.

Fluctuations

Parkinson disease patients usually have no evidence of cognitive fluctuations in the absence of dementia. On the other hand, Parkinson disease with dementia produces a pattern of impairment in reaction time, vigilance, and fluctuating attention that is comparable to dementia with Lewy bodies (Ballard et al. 2002a).

Autonomic Dysfunction

Autonomic dysfunction tends to occur in the late stages of Parkinson disease, and features such as orthostatic hypotension appear to be related to disease severity and duration. About one-third of patients have clinical features of autonomic dysfunction, although estimation of the prevalence of autonomic dysfunction is difficult in the presence of confounding factors such as the use of antiparkinsonian medications.

The most common autonomic features are decreased gastrointestinal mobility and bladder dysfunction. Constipation is very common, and serious complications such as intestinal pseudo-obstruction and toxic megacolon can occur. Bladder dysfunction with urgency, frequency, and incontinence and sexual dysfunction such as decreased libido and erectile dysfunction are other common features (Marti et al. 2003). Almost 60% of Parkinson disease patients have orthostatic hypotension (a fall in systolic blood pressure by ≥20 mm Hg) by tilt table testing, with decreased cerebral hypoperfusion, and approximately 20% of patients develop orthostatic symptoms related to reduced cerebral perfusion (Senard et al. 1997). This autonomic dysfunction appears to be secondary to impaired vagal control and hemodynamic response and correlates with disease duration (Orskov et al. 1987).

Preclinical Cognitive Impairment

In an incident cohort of Parkinson disease patients diagnosed over 2 years, 36% had cognitive impairment (Burn 2006). Early cognitive deficits are usually in visuospatial and executive function and verbal memory (Mahieux et al. 1998). These include decrements in planning, sequencing, concept formation, and working memory. Minor deficits in set shifting, retrieval of learned material, and reduced verbal fluency also are very frequent (McKeith 2000).

A more rapid rate of cognitive decline has been associated with the severity of motor symptoms (Levy et al. 2002). In particular, motor symptoms believed to be mediated by nondopaminergic mechanisms such as gait, speech, and postural control have been associated with accelerated decline in cognition (Aarsland et al. 2004). This can be explained by the fact that neurodegeneration within the cholinergic system mediates some of the nondopaminergic motor features in Parkinson disease with dementia and in dementia with Lewy bodies and also has a significant role in determining the cognitive and neuropsychiatric symptoms (Tiraboschi et al. 2000).

Neuropathology

Parkinson Disease With Dementia

The pathologicallogicalsubstrates for Parkinson disease with dementia include cortical Lewy bodies, Alzheimer pathology, or restricted subcortical pathology (Galvin et al. 2006). A recent study compared autopsy reports of 103 cases followed longitudinally showed three neuropathological profiles. Roughly one-third of Parkinson disease with dementia cases were associated with only neocortical Lewy bodies. Another third had abundant senile

plaques and neurofibrillary tangles meeting criteria for both Parkinson and Alzheimer disease. The final group had only brain stem pathology comprising Lewy bodies (Braak et al. 2005). This fits well with a recent staging paradigm proposed by Braak suggesting that Parkinson disease pathology begins in the lower brainstem and spreads in a caudal-to-rostral fashion (Braak et al. 2003).

The neuropathological hallmark of Parkinson disease with dementia is the presence of Lewy bodies and neuronal loss in the substantia nigra (Figure 11–1). In most cases, Lewy bodies are found in the dorsal motor nucleus of the vagus, the nucleus basalis of Meynert, the locus coeruleus, the raphe nuclei, the midbrain Edinger-Westphal nucleus, the olfactory bulb, medullary magnocellular reticular nuclei, pedunculopontine nucleus, thalamus, hypothalamus, autonomic ganglia, and in the cingulate and entorhinal cortex. Cell loss is seen in the substantia nigra as well as in the dorsal motor nucleus of vagus, nucleus basalis of Meynert, and the locus coeruleus.

Dementia with Lewy bodies, whether in a pure form or in combination with Alzheimer disease, appears to begin in a rostral fashion and spread caudally, whereas the pathology of Parkinson disease with dementia appears to begin in the brainstem and to spread rostrally (Braak et al. 2003). The later onset of dementia in Parkinson disease in relation to motor symptoms may be explained by the later involvement of the neocortical structures.

There is growing evidence that the dementia in Parkinson disease correlates best with Lewy bodies in the limbic and cortical areas, particularly in the entorhinal cortex and the cingulate cortex (Kovari et al. 2003).

Subcortical and nigral neuronal loss with Lewy body pathology can be associated with cognitive impairment in the absence of cortical Lewy bodies (Galvin 2006). In fact, a gradation of neuronal loss in the substantia nigra has been suggested, with dementia being associated with neuronal loss in the medial portion and motor signs being associated with neuronal loss in the lateral portions (Rinne et al. 1989).

Dementia With Lewy Bodies

Limbic and neocortical areas are preferentially involved in dementia with Lewy bodies with a variable degree of Lewy body pathology in the brainstem (McKeith et al. 2005). Cortical Lewy bodies have a predilection for the cingulate, entorhinal, and temporal cortex and the hypothalamus, basal forebrain, and amygdalae, with lesser involvement of the hippocampus and frontal and posterior cortical regions. The subcortical Lewy bodies are distributed in the dorsal motor nucleus of the vagus, the medullary magnocellular reticular nuclei, locus coeruleus, raphe nucleus, and midbrain tegmentum. Striatal Lewy bodies are relatively more abundant in dementia with Lewy bodies than Parkinson disease.

Over 70% of Lewy body patients have concurrent Alzheimer disease pathology. The neuritic plaques of Alzheimer disease include a dense core of $A\beta_{40}$, with neuritic processes composed of tau protein, but plaques in Lewy body disease are typically diffuse and composed primarily of $A\beta_{40}$. So called Lewy neurites are intracellular inclusions composed primarily of synuclein aggregates located in the neural processes. They are found in brain regions rich in perikaryal Lewy bodies and preferentially affect limbic and temporal lobe structures. Striatal Lewy neuritis in dementia with Lewy bodies may contribute to the extrapyramidal features.

In addition to the involvement of the central autonomic nuclei, recent evidence has pointed out involvement of the peripheral postganglionic autonomic neurons at an early stage in Lewy body disease (Tiraboschi et al. 2000). One study has shown a correlation between the presence of synuclein aggregates, thought to be pathological precursors of Lewy bodies, in the abdominopelvic autonomic neurons and diffuse cardiac sympathetic denervation (Taki et al. 2004).

Clinicopathological Correlates

The density of Lewy bodies in multiple brain regions correlates with the severity of cognitive impairment in Lewy body dementia independent of the degree of Alzheimer pathology. In addition, an association between Lewy neurite density and the degree of cognitive impairment has been suggested in dementia with Lewy bodies. The total Lewy body burden seems to correlate with disease duration. There is no clear evidence of correlation between specific clinical symptoms (cognitive fluctuations, parkinsonism, visual hallucinations, delusions, or falls) and the amount of Lewy body pathology in specific regions such as the neocortex, substantia nigra, or paralimbic area.

The memory deficit of Alzheimer disease predominantly represents a consolidation deficit and is thought to result from involvement of the medial temporal structures and their cortical connections. Although dystrophic neurites in the CA2–3 region of the hippocampus are commonly seen in dementia with Lewy bodies, its pathology tends to predominantly affect other regions such as the CA2–3 region, whose role in memory functions has not been defined. On the other hand, it is believed that the retrieval deficit of dementia with Lewy bodies is secondary to severe reduction in the dopaminergic projection to the striatum, with a possible neuromodulatory effect from cholinergic pathways on the septal dopaminergic deficit.

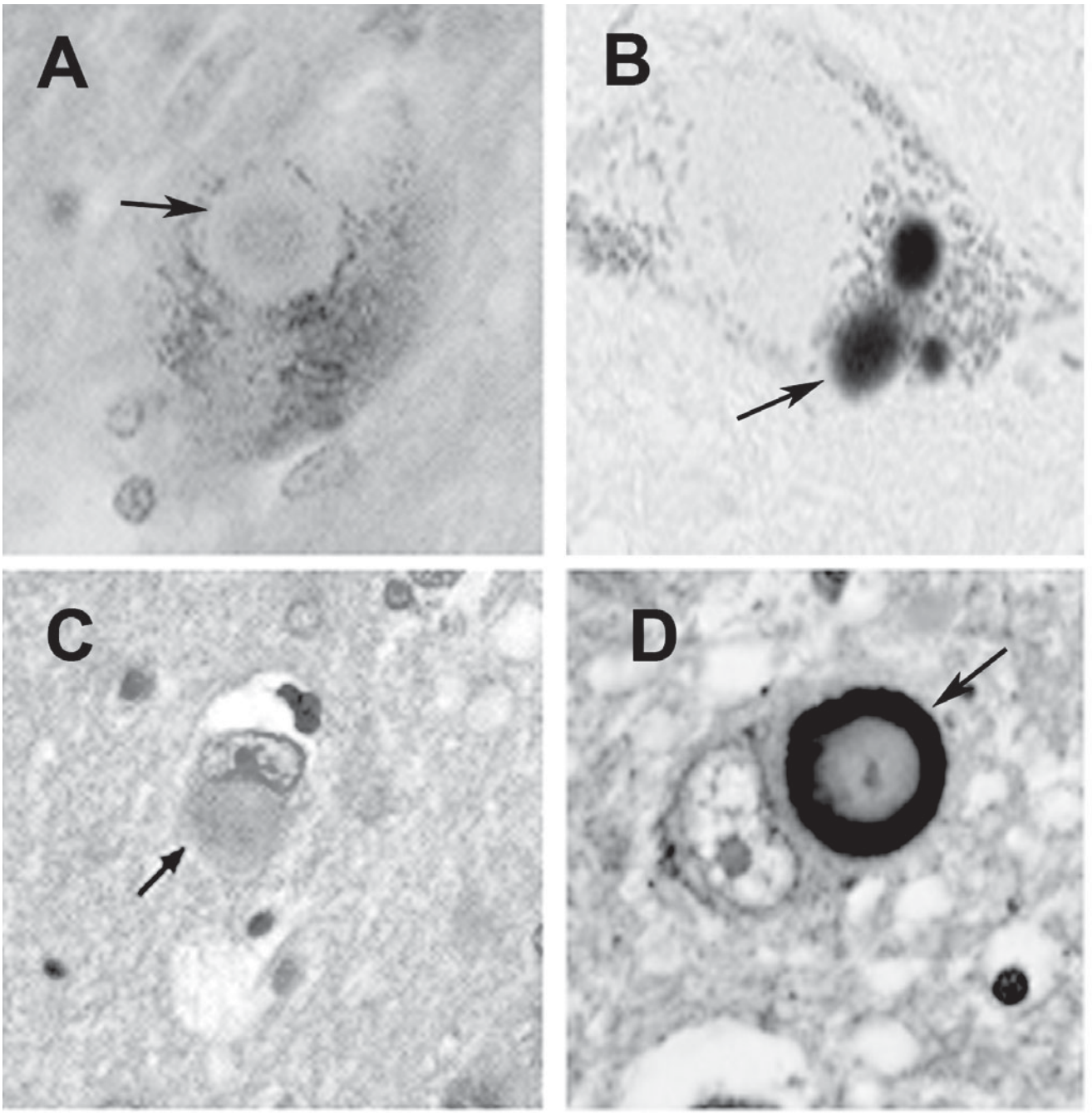

FIGURE 11–1. Photomicrographs of Lewy bodies. *(See color plate 9)*
Nigral Lewy bodies typically are round and have a pale halo surrounding an eosinophillic dense core. *Panel A* depicts a nigral Lewy body (arrow) after hematoxylin and eosin staining. *Panel B* demonstrates multiple nigral Lewy bodies detected with antibodies against α-synuclein. Cortical Lewy bodies *(Panel C),* on the other hand, tend to be eccentric and lack the defined core/halo appearance of nigral Lewy bodies with Hematoxylin and Eosin. With the advent of immunohistochemistry *(Panel D),* the use of antibodies against α-synuclein makes it easier to detect cortical Lewy bodies.

Dysfunction of the septal/diagonal band of Broca pathways to the hippocampus has been implicated in the memory impairment in Parkinson disease with dementia, whereas neuronal loss in the nucleus basalis of Meynert may account for other cognitive deficits such as impaired processing speed.

Consistent correlations between the severity of neuropsychiatric symptoms and Lewy body load have not been established. Visual hallucinations may be associated with the early specific visual perceptual deficits with disruption of the pathways for pattern/object recognition. Cholinergic deficits also seem to play a role. Nicotinic receptor

density measured by bungarotoxin binding (A7 subunit) is less in Lewy body patients with hallucinations than without. The more prominent elevation of muscarinic M1 receptor binding in Lewy body dementia patients who have delusions may be the result of receptor upregulation in the setting of severe presynaptic cholinergic depletion.

Many findings point to cholinergic depletion in the pathogenesis of fluctuations in dementia with Lewy bodies. These include evidence of depletion of neocortical acetylcholinesterase, corresponding basal forebrain cholinergic neuronal loss in Lewy body dementia compared with Alzheimer disease, and differences in nicotinic receptor binding in Lewy body patients with disturbed consciousness (Ballard et al. 2002b). The response of these patients to cholinesterase inhibitors (McKeith et al. 2000b) and the worsening of delirium with the use of anticholinergic agents (Flacker et al. 1998) support this concept. Similarly, Perry et al. (1999) demonstrated that the reduction of choline acetyltransferase in the temporal neocortex correlates with the degree of cognitive impairment in Parkinson disease with dementia but not with the degree of Alzheimer pathology.

The presumed pathophysiological mechanism of REM behavior disorder involves damage to the descending pontine-medullary reticular formation (including the magnocellular reticular formation) or sublaterodorsal nucleus that leads to a loss of the normal REM sleep inhibition of the spinal alpha-motor neurons. In humans, polysomnographic evidence of REM sleep without atonia is considered the electrophysiological substrate of RBD and is found in patients with or without florid RBD (Lai and Siegel 2003).

Neurochemical Changes

Although loss of the nigrostriatal dopaminergic pathway is mostly responsible for the motor features of Parkinson disease, the mesocorticolimbic dopaminergic system, which originates in the ventral tegmental area and projects to the limbic and prefrontal areas and to the caudate, may have a more important role in cognitive dysfunction. This is supported by evidence of decreased tyrosine hydroxylase immunolabeling in the prefrontal cortex. The degree of striatal dopamine reduction is comparable between Parkinson disease with dementia and dementia with Lewy bodies (Piggott et al. 1999). The loss of striatal and putaminal D_2 receptors in dementia with Lewy bodies may contribute to the neuroleptic sensitivity characteristic of these patients (McKeith et al. 1992a), whereas a compensatory increase in striatal D_2 receptors might be seen in the early stages of Parkinson disease.

Dementia with Lewy bodies and Parkinson disease with dementia are also associated with cholinergic dysfunction that occurs earlier and is more severe than the cholinergic dysfunction of Alzheimer disease. Presynaptic depletion in the brainstem and basal forebrain structures results in extensive cholinergic deficits and loss of postsynaptic mechanisms in Lewy body disease compared with Alzheimer disease (Perry et al. 1994). Severe losses of the basal forebrain acetylcholine can account for the hallucinations and fluctuations in arousal that characterize dementia with Lewy bodies. On the other hand, postsynaptic muscarinic receptors are better preserved and less functionally impaired in Lewy body dementia than in Alzheimer disease. This may be partly explained by the lower frequency of neocortical neurofibrillary tangles in dementia with Lewy bodies. Given the greater cholinergic deficit and the potentially more reversible changes, it has been hypothesized that Lewy body dementia patients might have greater benefit from the symptomatic and trophic effects of cholinergic stimulation than Alzheimer disease patients (Liberini et al. 1996).

A role for the noradrenergic system in the cognitive impairment of Parkinson disease is suggested by the greater degree of neuronal loss in the locus coeruleus in Parkinson disease with dementia than in nondemented Parkinson disease patients (Chui et al. 1986; Gaspar and Gray 1984). Neuronal loss in the locus coeruleus appears to correlate with measures of neuronal loss in the ventral tegmental area, medial substantia nigra pars compacta, and with more Lewy bodies in the anterior cingulate cortex in one study (Zweig et al. 1993). Loss of norepinephrine may account for reduced arousal during the off phases and the levels of norepinephrine metabolites have been shown to correlate with reaction time and vigilance (Litvan et al. 1991).

Diagnostic Evaluation

Structural Imaging

There are no radiological, biochemical, or clinically applicable genotypic markers that reliably distinguish dementia with Lewy bodies from other causes of dementia. However, radiological investigations may, along with other findings, help in supporting the clinical diagnosis (Table 11–5). In contrast to Alzheimer disease, there is little difference in the size of the hippocampus between Lewy body dementia patients and normally functioning elderly control subjects (Barber et al. 1999a). The relative preservation of the medial temporal lobes in Lewy body patients (Barber et al. 2000) is consistent with less severe memory impairment in Lewy body disease than Alzheimer disease. The degree of

ventricular enlargement or white matter changes in dementia with Lewy bodies is comparable to that of Alzheimer disease (Barber et al. 1999b). The presence of generalized atrophy or the rate of progression of whole brain atrophy is not helpful in the differential diagnosis.

Magnetic resonance imaging evidence of putaminal atrophy is seen in dementia with Lewy bodies but not in Alzheimer disease (Cousins et al. 2003). Whole brain and caudate volumes are significantly reduced in Alzheimer disease subjects compared with control subjects and Parkinson disease subjects, whereas both volumes are comparable between control subjects, Parkinson disease subjects, and Parkinson disease with dementia subjects. Despite these differences, caudate volumes do not seem to correlate with global cognitive function, executive performance, or processing speed (Almeida et al. 2003).

Functional Imaging

Functional brain imaging using [^{18}F]fluorodeoxyglucose (FDG)-PET or SPECT [^{99}Tcm]hexamethyl-propyleneamine-oxime (HMAO) shows only minor differences between dementia with Lewy bodies and Alzheimer disease (Higuchi et al. 2000; Rodriguez-Fernandez et al. 1998) (Table 11–5). However, FDG uptake studies show metabolic reduction in the visual association cortex in Lewy body disease that does not appear in Alzheimer disease (Higuchi et al. 2000).

Frontal and temporoparietal hypometabolism can be seen in PET studies of Parkinson disease with dementia patients, superimposed on the milder global hypometabolism seen in nondemented Parkinson disease subjects. The frontal hypometabolism has a positive correlation with working and executive deficits. In comparing Parkinson disease with dementia patients to Alzheimer patients, the former had greater resting state hypometabolism in the visual cortex and relatively preserved medial temporal metabolism. This pattern of temporal-parietal-occipital hypometabolism with relative sparing of the medial temporal may also be seen in dementia with Lewy bodies.

Functional brain imaging using [^{99}Tcm]HMAO and *N*-isopropyl-[^{123}I]p-iodoamphetamine ([^{123}I]IMP) SPECT in Parkinson disease shows reduced occipital perfusion as compared with other cortical areas (Matsui et al. 2005). Occipital hypoperfusion in SPECT can also be seen in dementia with Lewy bodies (Donnemiller et al. 1997). In fact, it has been suggested that reduced flow in the medial occipital lobe including the cuneus and the lingual gyrus can discriminate Lewy body dementia from Alzheimer disease, with a sensitivity of 85% and a specificity of 85% (Shimizu et al. 2005).

Cholinergic binding assessed by SPECT, using [^{123}I]IMP iodobenzovesimacol as a marker of vesicular acetylcholine transporter, is reduced in the parietal and occipital cortex in nondemented patients with Parkinson disease, whereas the binding decreases are more diffuse in Parkinson disease with dementia and similar to that of early-onset Alzheimer disease (Kuhl et al. 1996).

A dual PET approach (using the *N*-[^{11}C]methyl-4-piperidyl acetate [MP4A]) has shown that Parkinson disease with dementia patients have evidence of severe cholinergic deficits in the cortical regions in contrast with only a moderate degree in nondemented Parkinson disease patients (Hilker et al. 2005). In Parkinson disease with and without dementia, there is a correlation between cortical cholinergic denervation and performance on tests of attention and executive function (Bohnen et al. 2006). Reduced cortical acetylcholinesterase activity as measured by PET is more characteristic of Parkinson disease with dementia than Parkinson or mild Alzheimer disease (20%, 13%, and 9% respectively), compared with control subjects (Bohnen et al. 2003).

Functional studies of dopamine markers by SPECT and PET assess the presynaptic nigrostriatal neurons by evaluating the dopa decarboxylase activity, the dopamine transporter, and the postsynaptic dopamine D_2 receptor. PET scan using [^{18}F]dopa as a marker for dopaminergic function show loss bilaterally in the striatum, midbrain, and anterior cingulate area in dementia with Lewy bodies (Hu et al. 2000). Serial [123I]-N-3-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane and SPECT also demonstrate progressive striatal dopaminergic loss in both Lewy body dementia and Parkinson disease with dementia but not in Alzheimer disease. In fact, this finding may have a high specificity (94%) in distinguishing Lewy body dementia from Alzheimer disease. The loss of striatal and putaminal D_2 receptors in dementia with Lewy bodies may contribute to the neuroleptic sensitivity characteristic of these patients, whereas the lower incidence of these reactions in Parkinson disease with dementia may be explained by a compensatory increase in striatal D_2 receptors in the early stages.

Parkinson disease with dementia patients have lower *N*-acetylaspartate (NAA) levels in the occipital cortex by proton magnetic spectroscopy (Summerfield et al. 2002), and the levels seem to correlate with the degree of impairment. Although Alzheimer patients also have low levels of NAA, the levels of myoinositol, a marker of glial dysfunction, are elevated in Alzheimer disease but not in Parkinson disease with dementia.

Electrophysiological Studies

The electroencephalogram (EEG) shows diffuse abnormalities in most cases of dementia with Lewy bodies. EEG may show early slowing of dominant rhythms and epoch-

TABLE 11–5. Neuroimaging findings (structural and functional imaging) between dementias

Disorder	Pattern of atrophy on magnetic resonance imaging	Pattern of hypoperfusion (single photon emission computed tomography) or hypometabolism ([^{18}F]fluorodeoxyglucose–positron emission tomography)
Alzheimer disease	Maximal in hippocampi, generalized cortical atrophy evolves over time	Maximal in temporoparietal cortex
Parkinson disease	Minimal to no significant cortical or hippocampal atrophy	Normal or minimally abnormal
Parkinson disease with dementia	Minimal to no significant cortical or hippocampal atrophy	Maximal in frontoparieto-occipital cortex
Dementia with Lewy bodies	Minimal to no significant cortical or hippocampal atrophy	Maximal in parieto-occipital cortex

by-epoch fluctuations. Transient temporal slow wave activity is detected in 50% of cases (Briel et al. 1999).

Therapeutics

Cognitive Symptoms

Dementia with Lewy bodies is characterized by limbic and cortical cholinergic deficits that are more severe than in Alzheimer disease (Touchon et al. 2006). Augmentation of cholinergic function by inhibition of acetylcholinesterase appears to provide symptomatic benefits, although there are only a few clinical trials, and most guidelines are based on case reports and extension of therapeutic trials in Alzheimer disease. There is no compelling evidence that any one acetylcholinesterase inhibitor is better than any other. Attention, apathy, excessive somnolence, and hallucinations are most likely to benefit in dementia with Lewy bodies. In a double-blind, placebo-controlled, multicenter trial of 120 Lewy body dementia patients, subjects treated with rivastigmine 12 mg/day for 20 weeks had better performance on tests of attention, working memory, and episodic secondary memory than the placebo group (McKeith et al. 2000b). Patients given placebo showed a significant deterioration in attention at 12 and 20 weeks, whereas patients on rivastigmine performed above their baseline levels. A 24-week open-label study of galantamine in 50 patients showed improvement in visual hallucinations, nighttime behavioral, and fluctuating cognitive deficits. There was also a benefit in sleep abnormalities and REM behavior disorder (Edwards et al. 2007).

Anecdotal reports conflict as to whether memantine, which putatively diminishes the toxic effects of glutamate, produces benefit or worsens some symptoms of dementia with Lewy bodies (Ridha et al. 2005; Sabbagh et al. 2005).

Donepezil was evaluated in a randomized control trial involving 16 patients with Parkinson disease and dementia (Leroi et al. 2004). There was significant improvement in memory subscales and a trend toward improvement in psychomotor speed and attention. There were no differences in psychiatric status, motor activity, activities of daily living at baseline, or at the end points between the treatment and placebo groups. However, 25% of patients had side effects requiring withdrawal of the medication, including cholinergic side effects and worsening of parkinsonism. A double-blind, placebo-controlled crossover trial of 22 patients with Parkinson disease showed that donepezil was well tolerated and did not worsen motor signs, but cognitive benefits were limited to improvement in Mini-Mental State Examination scores (Ravina et al. 2005).

The American Academy of Neurology suggests the use of acetylcholinesterase inhibitors for the treatment of Parkinson disease with dementia (Miyasaki et al. 2006). A meta-analysis of donepezil, rivastigmine, and galantamine studies in Parkinson disease with dementia showed that 5.3% of patients showed improvement in outcome measures (cognition, global, behavior, functional), whereas 10.1% of patients on placebo treatment demonstrated worsening in outcome (Maidment et al. 2006).

Motor Symptoms

L-Dopa is the standard treatment for extrapyramidal symptoms in Parkinson disease. Yet, its use in dementia with Lewy bodies has been limited because of adverse effects on cognitive and behavioral features and worsening of psychosis. There have been reports of increased adverse events with the combined use of L-dopa and cholinesterase inhibitors in Parkinson disease (Okereke et al. 2004).

Some reports have suggested that dopaminergic treatment increases impulsivity or decreases performance, but neither of these side effects has been confirmed. L-Dopa replacement improves working memory in Parkinson disease patients, particularly visuospatial and object tasks (Costa et al. 2003), and dopamine withdrawal may unmask frontal lobe dysfunction in executive functions, spatial working memory, thinking time, and accuracy (Lange et al. 1992; Molloy et al. 2006). Dopamine agonists have been less effective and less well tolerated, with a higher incidence of drug-induced psychosis than with L-dopa. Therefore, a trial of L-dopa is recommended in dementia with Lewy bodies, with slow titration of the dose to symptomatic benefit.

Other Parkinson disease medications such as amantadine, catechol-*O*-methlytransferase inhibitors, monoamine oxidase inhibitors, and anticholinergics tend to exacerbate cognitive impairment. Cholinesterase inhibitors can worsen parkinsonism. In a study of rivastigmine in Parkinson disease, approximately 10% of patients had worsening of tremor, but their overall motor function was not significantly different between the treatment and placebo groups (McKeith et al. 2000b).

Behavioral Pathology

The first step in treating behavioral disturbances is assessment, including evaluation for physical factors that may be provoking behavioral disturbances, such as fecal impaction or other causes of discomfort or pain. Avoidance of or reduction of doses of other medications that potentially may cause agitation should also be attempted. Anxiety and depression are common in Lewy body and Parkinson disease dementia, and both groups appear to respond to selective serotonin reuptake inhibitors and anxiolytics, although this has not been rigorously studied. Medications used to modify behaviors should be used for the shortest duration possible. Benzodiazepines are better avoided given their risk of sedation and paradoxical agitation.

Nonpharmacological Approaches

Education of caregivers is an essential part of managing behavioral pathology. Often, these behaviors are reactions to external stimuli that can be identified and reduced or eliminated. Isolation in the form of sensory deprivation is probably underrecognized, and providing hearing aids or visual aids can often be helpful.

Responses to patients should include reassurance, validation of their concerns, and avoiding correcting perception and reality orientation. Caregivers should be educated about the importance of remaining calm when around the patient.

Modifying patients' environment includes reducing noise, increasing illumination, and reducing restraints. Patients often benefit from provision of structure and routine through exercise and social activities. The tasks should be guided and manageable by the patient to avoid his or her frustration.

Hallucinations and delusions need not be confronted. Validation of the patients' feelings and reassurance that their concerns are taken seriously can be calming. Caregivers should learn to avoid confrontation and arguing.

Although education can provide caregivers with better understanding of the nature of the condition and improve their skills in managing difficult situation, they should also be made aware of available support systems. (See also Chapter 17 of this volume, "Behavioral and Environmental Management," for more on the topic of nonpharmacological approaches.)

Acetylcholinesterase Inhibitors

A meta-analysis of six large trials in Alzheimer disease showed a small but significant benefit in treating neuropsychiatric symptoms (Trinh et al. 2003). Psychosis, agitation, wandering, and anxiety are the most consistently responsive, whereas depression, apathy, and eating behaviors are less responsive. Fewer reports are available for behavioral improvement with the use of the cholinesterase inhibitor rivastigmine in dementia with Lewy bodies. In a large multicenter trial, rivastigmine resulted in improvement by 30% from baseline in psychiatric symptoms (McKeith et al. 2000b).

Antipsychotics

Visual hallucinations occur in up to 80% of patients with Lewy body dementia and have been suggested as predictors of a good response to cholinesterase inhibitors (McKeith et al. 2004). The management of psychosis in dementia with Lewy bodies has been mostly based on Alzheimer disease trials and follows the general guidelines of pharmacotherapy of elders (Kaufer 2002). In addition, some recommendations for the use of antipsychotics in Lewy body dementia are based on studies in Parkinson disease because of its similar synuclein pathology. It can be very challenging given the sensitivity of these patients

to antipsychotics as well as the complex neurochemical and pathological deficits with wide phenotypic variations.

Dopaminergic agents are probably only exacerbating factors in patients with predisposition to psychosis. The dose, duration, or number of dopaminergic agents does not seem to relate to the risk of psychosis in Parkinson disease (Aarsland et al. 1999a).

The first approach is to attempt reduction of dopaminergic agents. So called typical neuroleptics such as haloperidol and atypical neuroleptics with D_2-receptor antagonism (such as olanzapine and risperidone) should be avoided because of the risk of neuroleptic malignant syndrome, parkinsonism, somnolence, and orthostatic hypotension. Experience with atypical antipsychotics in Lewy body disease has been mixed. Risperidone and olanzapine have been shown to reduce psychosis and agitation in Alzheimer disease in randomized trials. Although low doses of risperidone (0.5 mg) and olanzapine (2.5 mg) are usually well tolerated, they may aggravate extrapyramidal symptoms of dementia with Lewy bodies (Walker et al. 1999), especially in advanced cases. Quetiapine frequently is used for psychosis in dementia with Lewy bodies. Efficacy and tolerability have been documented in both Parkinson disease and dementia with Lewy bodies (Fernandez et al. 2002, 2003).

Sleep Disorders

Clonazepam is the usual therapy for REM behavior disorder, at 0.25–0.5 mg/night, but doses above 1 mg nightly are necessary in some patients. Melatonin may also offer some benefit as monotherapy or in conjunction with clonazepam. Boeve et al. (2004) reported persistent efficacy beyond 1 year with melatonin. Melatonin may reduce the percentage of REM sleep without muscle atonia and decrease the number of stage shifts in REM sleep, suggesting it has more direct mode of action on REM sleep pathophysiology (Boeve et al. 2004). Other drugs reported to improve RBD include pramipexole, donepezil, L-dopa, carbamazepine, triazolam, clozapine, and quetiapine.

Treatment for insomnia can be attempted with low doses of benzodiazepines, such as zolpidem, or trazodone. These medications have not been extensively studied in Lewy body disease and daytime sedation is a potential side effect. For excess daytime sleepiness, treatment options include buproprion, modafinil, or psychostimulants.

Autonomic Dysfunction

Management of orthostatic hypotension includes measures such as leg elevation, elastic stockings, increasing salt and fluid intake, and avoiding medications that exacerbate orthostasis. If these measures fail, midodrine or fludrocortisone can be used. Midodrine is a vasoconstrictor with side effects of urinary retention and supine hypertension. Fludrocortisone increases fluid retention.

Supine hypertension is a common manifestation of autonomic dysfunction and can lead to serious complications, including left ventricular hypertrophy and strokes. Treatment of supine hypertension is difficult, and multiple trials of different medications may be required. Simple measures include avoiding the supine position in the daytime and using a tilt-up position at night, which will decrease nocturnal natriuresis and may also help improve orthostatic hypotension in the morning. Medications are often required to decrease nocturnal diureses by decreasing blood pressure at night. However, these agents should have short half lives to avoid precipitating hypotension in the morning. Transdermal nitroglycerin patches at doses of 0.1–0.2 mg/hour are a safe option and can be removed on sitting up. Antihypertensive agents have been tried with variable success. However, they do not improve nocturnal natruiresis and have a higher risk of inducing orthostatic hypotension.

Bladder dysfunction in Lewy body and Parkinson disease is often associated with nocturia, urgency with or without urge incontinence, and detrusor hyperreflexia. Decreasing fluid intake in the evening can often improve nocturia. Medications with anticholinergic activity can be used to treat urinary urgency, frequency, and urge incontinence, but they can exacerbate cognitive problems. Other risks include precipitating orthostatic hypotension if used early in the day. Although these medications are effective for detrusor hyperreflexia , they may worsen urine retention in patients with detrusor hyporeflexia or flaccid bladder, which is more common in multisystems atrophy patients, in whom detrusor hyperreflexia is more common. Another precaution concerns men, who often have concomitant prostate hypertrophy or bladder outlet obstruction. Anticholinergics should be avoided in this group and urine retention should be prevented by intermittent catheterization.

Constipation can usually be treated by exercise and dietary modifications with at least two high-fiber meals each day. Laxatives such as lactulose in dosages of 10–20 mg/day can be helpful, but mechanical disimpaction may be needed in severe cases. Cholinergic stimulation by acetylcholinesterase inhibitors used for cognitive treatment might improve constipation in some patients.

Although autonomic dysfunction plays a major role in impotence, there is often contribution from depression and nocturnal akinesia. Treatment often requires specialized care with a urologic consultation. A small bedtime dose of L-dopa might alleviate bradykinesia and increase libido. On the other hand, high doses of dopaminergic medications might induce hypersexuality and inappropri-

ate behavior. If mood disturbances and depression are associated with the sexual dysfunction, therapy with antidepressants can be considered.

Conclusion

Dementia with Lewy bodies and Parkinson disease dementia are common causes of cognitive, behavioral, affective, movement, and autonomic dysfunction in older adults. They are associated with the accumulation of Lewy bodies in subcortical, limbic, and neocortical regions and characterized clinically by a progressive dementia, parkinsonism, cognitive fluctuation, and visual hallucinations. There is essentially no difference in the clinical phenotype between the two clinical entities. The presence of neocortical Lewy bodies imparts a distinctive clinical phenotype that is well captured by published criteria regardless of temporal relationship of motor to cognitive symptoms. We can now begin to widen the spectrum of our understanding of neurodegenerative diseases and change concepts of Lewy body disease from a movement disorder to a disorder associated with wider neuropsychiatric disturbances, impaired cognition, episodic confusion, and the development of dementia. As our ability to refine clinical and cognitive profiles of Parkinson disease with dementia and dementia with Lewy bodies increases, the development of pharmacotherapeutic agents that may be more selective or potentially specific for these syndromes becomes more possible.

KEY POINTS

- The synucleinopathies are characterized by α-synuclein-containing intraneuronal inclusion bodies called Lewy bodies.
- The diseases associated with Lewy bodies are the second largest group of dementing illnesses; their clinical manifestation depends on the distribution of Lewy bodies in the central and autonomic nervous system.
- The most common Lewy body diseases are Parkinson disease, Parkinson disease with dementia, dementia with Lewy bodies, and multiple systems atrophy.
- These diseases have in common a degree of cognitive impairment, extrapyramidal symptoms, neuroleptic sensitivity, sleep disorders, and dysautonomia.
- Dementia with Lewy bodies is probably the second most common cause of dementia; however, it remains an underdiagnosed cause of dementia.
- The diagnosis of probable dementia with Lewy bodies requires the presence of dementia with at least two of three core features: cognitive fluctuations, recurrent visual hallucinations, and spontaneous parkinsonism.
- The cognitive profile of dementia with Lewy bodies and Parkinson disease with dementia is very similar; the main differentiation is the temporal sequence of dementia and motor involvement.
- Dementia with Lewy bodies and Parkinson disease with dementia have prominent involvement of executive function, attention, and visuospatial skills.
- Cholinesterase inhibitors are used to treat the cognitive and behavioral pathology of dementia with Lewy bodies.

- Neuroleptic sensitivity is a serious, unpredictable, and potentially fatal side effect in this group of patients.
- If L-dopa is used to treat the motor symptoms of dementia with Lewy bodies, the dose should be titrated gradually to avoid the risk of worsening psychosis.

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CHAPTER 12

Frontotemporal Dementia

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In its broadest sense, the term *frontotemporal dementia* (FTD) refers to a number of neurodegenerative diseases that vary in clinical presentation and pathological findings. FTD is also known as frontotemporal lobar degeneration (FTLD) (Neary et al. 1998) or Pick complex (Kertesz et al. 2003). The clinical and research nosologies for this disease continue to evolve and are sometimes controversial and can be confusing. In this chapter, the term *FTD frontal variant,* or *fvFTD,* is used as needed for clarity when referring to the specific FTD clinical subtype characterized by executive dysfunction and apathy. Although the clinical syndromes vary, they characteristically involve problems with language, behavior, and/or motor findings, such as parkinsonism. Research in FTD, including genetic discoveries and the application of modern neuroimaging techniques, has led to remarkable advances in the understanding not only of this dementia but other dementias and neurological illnesses.

History

The archetypal FTD is Pick disease, first clinically delineated by Arnold Pick (1892), who described language impairments and behavioral disturbances in the setting of focal atrophy. Alzheimer (1911) made the first histopathological description of Pick disease with argyrophilic inclusions (later called Pick bodies) and swollen, achromatic cells (later called Pick cells). The Lund-Manchester criteria (Lund and Manchester Groups 1994) delineated the clinical features of FTD; these criteria were later refined by a consensus panel that used the term *frontotemporal lobar degeneration* (Neary et al. 1998). Additional clinical consensus criteria for FTD have been published (McKhann et al. 2001).

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Epidemiology

Whereas Alzheimer disease usually occurs in individuals over age 65 years, FTD occurs, on average, in individuals in their 50s and may represent the most common cause of dementia in this age group (Knopman et al. 2004; Ratnavalli et al. 2002). A study in Cambridge, England (Ratnavalli et al. 2002), found a prevalence of FTD of 15 per 100,000, which was equal to that of Alzheimer disease, in the 45- to 65-year-old age group. For individuals with dementia onset at age 55 years or younger, FTD may be more prevalent than Alzheimer disease. The mean age at onset of FTD in this study was 52.8 years. Onset before age 65 years is one of the clinical diagnostic criteria for FTD (Neary et al. 1998). The literature generally shows that survival is shorter in FTD than in Alzheimer disease (Hodges et al. 2003; Lipton et al. 2003; Roberson et al. 2005). Hodges et al. reported median survival from symptom onset and from diagnosis as about 6 years for fvFTD and about 3 years for FTD associated with motor neuron disease (FTD-MND). The disease duration for FTLD with clinical motor neuron disease is shorter than that for FTLD with motor neuron–type inclusions (Josephs et al. 2005).

Clinical Subtypes

Patients with FTD may present with a behavioral syndrome, the FTD frontal/behavioral variant (Gustafson 1987; Neary et al. 1988), or with a language variant, primary progressive aphasia (Mesulam 1982; Weintraub et al. 1990), which subsumes progressive nonfluent aphasia and semantic dementia (Hodges et al. 1992; Snowden et al. 1989). All are characterized by an insidious onset, generally prior to age 65 years and typically in the fifth or sixth decade of life, with gradual progression of disease.

Frontal Variant Frontotemporal Dementia

The frontal variant of FTD, fvFTD, is an FTD subtype characterized by executive dysfunction, social and interpersonal conduct problems, and apathy and/or disinhibition. It is sometimes referred to solely as FTD or, more descriptively, as the FTD behavioral variant. The behaviors cited in this section are characteristic of fvFTD but may overlap with language presentations of FTD as well. These behaviors are associated with abnormalitites of the right frontotemporal lobes on neuroimaging (Mychack et al. 2001). Patients with orbitofrontal dysfunction are more "disagreeable" and less modest and altruistic (Rankin 2004). Damage in the ventromedial frontal lobes is associated with disinhibited, impulsive, antisocial, and compulsive behaviors (Rosen et al. 2000).

Lack of insight is a hallmark of the fvFTD subtype. Anosognosia often occurs, such that an individual is unaware of deficits. Patients are often impulsive and oblivious to societal or other limitations on their actions. Inappropriate, disinhibited, and sometimes even criminal, behaviors, including stalking, have been reported, as in the following case example:

Case 1

Mrs. A developed personality changes in her 50s. Her grown daughters described her as having been a happy, loving mother/homemaker and upstanding citizen prior to the onset of her illness. One day, she saw a young man (who did not appear disabled) park his sports car in a handicapped spot. She became angry at his presumed flouting of the parking regulations and proceeded to scratch his vehicle with her keys and attempted to scratch his face as well. Assault charges were filed but later dropped because of the circumstances of her illness. She also had the hyperphagia and weight gain often exhibited by patients with FTD, especially the frontal variant, early in the course of their illness. This patient overate and gained weight and dress sizes, but when her daughters took her shopping for new outfits, she insisted that she was her previous size, despite all evidence to the contrary, and would refuse to try on or buy larger sizes. Her daughters surreptitiously purchased new clothes for her in the correct size and removed the labels, so that the patient had items that fit.

Patients with FTD frequently eat to excess, sometimes multiples of the same item, in a day, even things they previously detested. One patient reportedly disliked bananas but began to eat around 10 a day with the onset of her illness. Carbohydrate cravings are also common. Patients may consume vast quantities of junk food, eating whole boxes of cookies or large bags of chips or drinking several liters of soda daily. Patients may also drink alcohol to excess, even with no prior history of problems with alcohol.

The concept of payment for goods is often lost, and patients with the FTD clinical profile may shoplift, sometimes trivial items or things they already own. In the aforementioned case example, the same woman walked out of a store wearing a new pair of shoes for which she had not paid. Her explanation was that she had left her old pair of shoes, thinking that this "trade" was adequate. On the other end of the behavioral spectrum, apathy and emotional blunting may occur in conjunction or independently of disinhibition. A father with fvFTD attended his daughter's wedding and walked her down the aisle "with-

out cracking a smile the entire time." Changes in hygiene often occur, as in the following case example:

Case 2

Ms. B, a woman in her 40s who was a clerical worker for a trucking company, had been named the national employee of the year. The following year, she became very apathetic and quit working and showering or bathing. She sometimes walked the neighborhood in her pajamas and picked through neighbors' trash cans. She was hospitalized on a psychiatric unit and diagnosed with possible schizophrenia until a head computed tomography was performed that showed severe bifrontal atrophy, which led to a neurological consultation and the diagnosis of Pick disease and, eventually, fvFTD.

Compulsive and hoarding behaviors may occur. One patient with fvFTD accumulated golf balls in large boxes, including 300 he picked up on a single hot Texas summer day (>100°F). A woman with fvFTD packed a suitcase for a trip out of state with nothing but books; this was one of the initial symptoms alerting her family to a problem. Her husband later found her to be hoarding library books under their bed and other places at home.

Primary Progressive Aphasia

Patients with a language variant of FTD, either progressive nonfluent aphasia or semantic dementia, frequently have one or more extensive evaluations for stroke caused by their aphasia. The aphasia worsens and they may become mute. Some also develop behavior problems.

Progressive Nonfluent Aphasia

Progressive nonfluent aphasia involves expressive aphasia with word-finding difficulty, agrammatism, and phonemic paraphasias. A schoolteacher who became unable to lecture was still able to work as a cashier. She and her husband were able to continue ballroom dancing for about 5 years after the onset of her aphasia, until she developed parkinsonian symptoms (including falling backward) and memory problems (such that she was forgetting dance steps). Unlike the other forms of FTD, progressive nonfluent aphasia patients usually have little functional or behavioral impairment until late in their disease. As in this patient, parkinsonism may emerge as the disease progresses.

Semantic Dementia

Semantic dementia, also called the temporal lobe variant of FTD (tvFTD), is caused by a progressive loss of information about the world associated with degeneration of the anterior temporal lobes. It usually manifests as a fluent dysphasia with impairment of semantic verbal memory (severe difficulty in naming and in understanding the meaning of words) and an associative agnosia (e.g., difficulty in stating or demonstrating the function of an object such as a tool or utensil) in individuals with more left temporal lobe involvement. Prosopagnosia (inability to recognize faces) may rarely occur and is associated with right temporal lobe damage. More commonly, behavioral problems similar to fvFTD occur in individuals with more right lobar dysfunction, as in the following case example:

Case 3

A retired personnel director had gradual onset of language decline and loss of information about the world at age 64 years. For example, he became unable to comprehend the meaning of a traffic stop sign. He was diagnosed with dementia of uncertain type. At age 71 years, he still worked part-time in a retail clothing store but was having difficulties in job performance. He had behavioral symptoms, including disinhibition, agitation, and verbal and physical aggression. He was evaluated by a dementia specialist who found him unable to name or comprehend colors, types of clothing, and clothing parts (e.g., sleeve). He was diagnosed with semantic dementia, and his family arranged for him to quit working and driving per the doctor's recommendation. The patient had anosognosia and did not understand why he could no longer work.

Artistic abilities often manifest in patients with a language variant of FTD, but they may emerge in patients with nonlanguage presentations of FTD as well (Miller et al. 1998). These talents may manifest de novo or as a modification of a skill previously evident in an individual.

Overlap of Frontotemporal Dementia Clinical Syndromes

Because the three FTD clinical syndromes often overlap (as can be seen in some of the above examples), and because they may also overlap motor syndromes such as motor neuron disease/amyotrophic lateral sclerosis (ALS) and parkinsonism (including corticobasal syndrome and progressive supranuclear palsy), certain authors suggest the term *Pick complex* has been suggested to encompass all of these syndromes (Kertesz and Munoz 1998; Kertesz et al. 2003).

The current clinical criteria for FTD have been criticized by a number of authors for their lack of precision and poor correspondence with autopsy-determined diag-

noses. One autopsy-based retrospective study found that most patients with FTD met clinical diagnostic criteria for Alzheimer disease (Varma et al. 1999). Another study reported that 18 of 21 patients with autopsy-proven Pick disease were misdiagnosed clinically as having Alzheimer disease (Mendez et al. 1993). The current clinical criteria for FTD fail to account for many neurogenetic and neuroimaging aspects of the diagnosis of FTD. Rosen et al. (2002) found that the Neary et al. (1998) clinical consensus criteria efficiently separated 30 autopsy-proven cases of Alzheimer disease and 30 autopsy-proven cases of FTLD. They found that five clinical features best distinguished FTLD from Alzheimer disease: presence of social conduct disorders, hyperorality, and akinesia and absence of amnesia and absence of a perceptual disorder. However, Knibb et al. (2006) reviewed the literature since the introduction of diagnostic consensus criteria in 1996 and found the criteria lacking. For individual patients with FTLD, core features were not consistently found while exclusionary criteria, such as impaired episodic memory, sometimes were present. These authors also point out that imaging is sometimes crucial for diagnosis and suggest that revisions to the consensus criteria are warranted.

Neuropsychological, Functional, and Behavioral Measurement in Frontotemporal Dementia

Tests such as the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) are insensitive to the early and isolated executive and/or language deficits of FTD patients (Gregory et al. 1997); however, studies have shown that MMSE scores decline at a greater rate in FTD than in Alzheimer disease (Chow et al. 2006; Rascovsky et al. 2005). Other rating scales such as the Neuropsychiatric Inventory (Cummings et al. 1994) and Clinical Dementia Rating (Morris 1993) are more sensitive to early disease. Other tests sensitive to FTD include the Frontal Behavioral Inventory (Kertesz et al. 1997), the Frontal Assessment Battery (FAB) (Dubois et al. 2000), and Adenbrooke's Cognitive Examination (ACE) (Mathuranath 2000). The ACE has high reliability and sensitivity in relatively young subjects with FTD who had mainly primary progressive aphasia and language involvement. In addition, using higher cutoff values for scores yielded false-positive results in which Alzheimer disease was classified as FTD. Moreover, the ACE is culturally specific to the United Kingdom because it includes questions such as naming the leader of the opposition in the British Parliament.

The FAB has been shown to distinguish healthy control subjects from patients with mild Parkinson disease, multiple system atrophy, corticobasal degeneration (CBD), and progressive supranuclear palsy. Subscores of the FAB have been shown to differentiate FTLD from Alzheimer disease (Lipton et al. 2005). Specifically, the FTLD group scored lower on tasks of mental flexibility and environmental autonomy, and the Alzheimer disease group scored lower on a motor programming task (the Luria maneuver). Tasks used in the FAB and other tests may be incorporated usefully into a clinical evaluation to assess frontal lobe function. However, caution should be used in interpreting the results. For example, patients may be asked to perform the Luria maneuver, in which they imitate the examiner in making a "fist-cut-slap" series of hand gestures (making a fist, then placing the hand perpendicularly as in a handshake, and then turning the hand palm downward). The examiner should perform the sequence of movements two or three times with the patient and then ask the patient to continue with the pattern. The Luria maneuver is considered a test of frontal lobe function; therefore, patients with severe frontal lobe dysfunction will have difficulty even imitating the examiner on this motor program. However, the aforementioned study of FAB showed that patients with Alzheimer disease actually performed worse on the Luria maneuver than patients with FTLD. The Lipton et al. (2005) confirmed that patients with FTD, particularly the FTD clinical profile, will often display echopraxis (imitating the examiner), perseveration, and motor impersistence. Patients can also be tested for frontal release signs as described in Chapter 4 of this volume, "Medical Evaluation and Diagnosis."

Clinical Syndromes Associated With Frontotemporal Dementia

Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

The incidence of dementia in ALS was formerly reported to be quite low (e.g., 5% [Strong and Grace 1998]). The predominant form of dementia in ALS is FTD. Of 100 ALS patients studied prospectively with extensive neuropsychological assessment, about one-third met criteria for FTLD (Lomen-Hoerth et al. 2003). Many patients with FTLD have motor neuron–type inclusions on histopa-

thology, either with or without clinical motor neuron disease. These and other pathologic similarities provide additional evidence for linkage of FTLD and ALS (Bigio et al. 2003). The disease duration for FTLD with clinical motor neuron disease is shorter than for FTLD with motor neuron–type inclusions (Josephs et al. 2005). Linkage to chromosome 9q21-q22 for familial ALS patients with FTD has been reported (Hosler et al. 2000).

Corticobasal Syndrome

FTD and corticobasal syndrome (also sometimes referred to as corticobasal degeneration [CBD], particularly in autopsy specimens) classically have been regarded as clinically distinct entities (Lang et al. 1994; Watts et al. 1994). CBD was originally defined as a Parkinson-plus syndrome that tends to progress more rapidly than Parkinson disease and is usually less amenable to treatment. The authors of the first description of corticodentatonigral degeneration (later renamed CBD) did, however, recognize the resemblance of the pathology to Pick disease (Rebiez et al. 1968). CBD is usually reported to be clinically characterized by unilateral rigidity, apraxia, alien hand syndrome, reflex myoclonus, and cortical sensory loss (Riley et al. 1990).

Retrospective neuropathological studies have shown that patients with clinically diagnosed FTD may have pathologic findings of CBD and vice versa (Boeve et al. 1999; Kertesz et al. 2001; Schneider et al. 1997). Movement disorders specialists may overlook the dementia, whereas neurobehavioral or psychiatric specialists may overlook problems such as parkinsonism. Prospective study of clinically diagnosed FTD and CBD with neuroimaging and pathologic examination is crucial in refining the clinical diagnosis of these diseases, in raising awareness of their overlap, and in refining treatment. Whether FTD, Pick disease, and CBD are distinct entities, overlapping entities, or the same entity remains controversial (Neary 1997).

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is another Parkinson-plus syndrome that has clinical and pathologic overlap with FTD. Both may be pathologically classified as abnormalities of the cyoskeletal protein *tau* (e.g., tauopathies), and the dementia of PSP may be clinically classified as FTD. This disorder begins in late life and is characterized by balance difficulty, falls, visual disturbances, slurred speech, dysphagia, and personality change (Richardson et al. 1963). Dementia tends not to be pronounced. A characteristic triad of ophthalmoplegia, pseudobulbar palsy, and axial dystonia develops. First, downward gaze is impaired, then upward gaze, then voluntary gaze in all directions. If the eyes are fixed on a target and the head is turned, full eye movement occurs (doll's eye phenomenon), indicating that the motor nerves are intact.

The etiology of this disease is unknown. Pathological findings include loss of neurons, gliosis, and the presence of neurofibrillary tangles in the surviving neurons in the midbrain, cerebellar peduncles, and subthalamic nucleus. Functional impairment proceeds to anarthria and total immobility.

Neuropathology

FTD is considered to be pathologically distinct from Alzheimer disease in most cases. Historically, the FTD disorders have been divided into Pick disease and non-Pick lobar atrophy (Dickson 1998; Hulette and Crain 1992). The different subtypes of FTD share some neuropathological features. Both have grossly appreciable frontal and temporal atrophy. Microscopically, frontotemporal degeneration is characterized by upper cortical microvacuolation, variable caudate nucleus atrophy and nigral pallor, superficial cortical microvacuolation and gliosis in the frontal and/or temporal lobes, and variable ballooned neurons in the cortex and amygdala (Brun 1987, 1993). Pick bodies (round to oval argyrophilic, tau- and ubiquitin-positive neuronal cytoplasmic inclusions in the hippocampal dentate gyrus and neocortex) are seen only in Pick disease. Non-Pick lobar atrophy recently has been subclassified on the basis of the presence or absence of newly discovered immunohistochemically distinct inclusions (Bergeron et al. 1998; Cooper et al. 1995; Jackson and Lowe 1996).

In the nonfamilial non-Pick lobar atrophies, there are at least three separate diagnostic categories. They are defined by the presence or absence of specific tau and ubiquitin inclusions in the hippocampal dentate gyrus and/or superficial frontal and/or temporal cortex. Differences in tau and ubiquitin immunohistochemistry are important in classifying pathologic FTD subtypes. The chief protein associated with ubiquitinated inclusions is now recognized to be trans-activation-response (TAR)-DNA-binding protein 43 (Neumann et al. 2006). One subtype is motor neuron type dementia (frontotemporal degeneration with ubiquitinated inclusions, also called *motor neuron inclusion dementia),* which has ubiquitin-positive, tau-negative inclusions in the hippocampal dentate nucleus and in neocortical neuronal layers II and III. CBD has tau-positive neuronal inclusions and glial plaques, along with ballooned neurons, in the cortex, basal ganglia, brainstem, and cerebellum. Frontotemporal degeneration with

neuronal loss and spongiosis (also known as dementia lacking distinctive histopathology) (Knopman 1993) has no tau or ubiquitin inclusions, but some of these cases have been classifiable as FTLD-MND on the basis of current pathological criteria for FTD (Lipton et al. 2004).

Despite the shared pathology in FTD, there may be a variety of pathological findings within the same clinical FTD subtype (Munoz 1998). These include classic Pick disease with Pick bodies and Pick cells, frontal degeneration with microvacuolation and gliosis, ubiquitin-positive inclusions similar to those found in motor neuron disease (with or without anterior horn cell disease), familial cases with tau mutations with neuronal and glial tau inclusions, and CBD.

Familial multiple system tauopathy is one of the many cases of familial FTD and parkinsonism linked to chromosome 17 (FTDP-17). These families have a variety of clinical presentations, including disinhibition-dementia-parkinsonism-amyotrophy complex, and neuropathological findings always associated with tau deposition. In contrast, individuals with progranulin mutations, an even more common form of autosomal dominant FTD, are found to have ubiquitin pathology at autopsy.

Validity of the FTLD diagnostic consensus criteria has been verified histopathologically (Knopman et al. 2005). Large pathological studies suggest that motor neuron–type, ubiquitin-positive inclusions are the most common histopathological type of frontotemporal lobar degeneration (Josephs et al. 2004; Lipton et al. 2004). This varies substantially by clinical syndrome.

Diagnostic Tests

Clinical evaluation, including history from a reliable collateral source, such as a close family member, is crucial in the diagnosis of this illness. Family history of neurological disease and psychiatric illness is important because FTD may be hereditary and is often not diagnosed as FTD per se. For example, one patient with FTD had no known family medical history of FTD but had a grandfather who was institutionalized in a state mental hospital after a number of unusual behaviors beginning in his 50s, including setting his wife on fire. Neurological evaluation may elicit abnormalities, such as motor weakness, parkinsonism, or frontal reflexes, that may provide additional diagnostic certainty.

Neuropsychological Testing

Neuropsychological evaluation is often helpful in the diagnosis of FTD. Usual clinical tests, such as the MMSE, do not directly assess executive functioning and may be relatively normal in patients with FTD (because of the relative sparing of memory) or may show profound impairment in patients with the language variants of FTD. Neuropsychological evaluation may reveal executive dysfunction on commonly performed assessments including the Stroop Category Test, Trail Making Test, verbal and design fluency, and the Wisconsin Card Sorting Test (Hodges and Graham 2001).

Cognitive speech-language evaluation is often helpful, especially to specifically diagnose language variants. Some patients and families may also benefit from further therapy to assist in maintaining communication.

Neuroimaging

Prominent atrophy on structural MRI scans is a common feature of FTD, particularly in individuals without motor neuron disease (Figure 12–1). Neuroimaging with fluorodeoxyglucose positron emission tomography (FDG-PET) is sometimes helpful in the differential diagnosis of FTD (Foster et al. 2007) and is Medicare-approved for this purpose, so long as certain qualifications are met. (See also Chapter 6 of this volume, "Neuroimaging.") The amyloid imaging agent Pittsburgh Compound B (PIB) may even be more valuable for ruling out atypical forms of Alzheimer disease that mimic FTD (Rabinovici et al. 2007).

Electroencephalography

Electroencephalography is not generally helpful for diagnosis of FTD because it has been shown to be normal in many cases. One study showed electroencephalographic abnormalities correlate with severity of FTD, but this was not helpful in differentiating it from Alzheimer disease (Chan et al. 2004).

Genetics

Genetic tests are not available commercially but are a major area of research interest. Multiple genetic loci (on chromosomes 3p, 9p, 9q, 17q21, and 17q24) and four genes (microtubule-associated protein tau, progranulin, valosin-containing protein, and charged multivesicular body protein 2B) have been associated with inherited frontotemporal lobar degeneration (Bugiani 2007; Mackenzie and Rademakers 2007; Rademakers and Hutton 2007). FTD with parkinsonism (FTDP-17) has been linked to mutations in the gene coding for the microtubule-associated protein tau (Hutton et al. 1998; Poorkaj et al. 1998; Spillantini et al. 1998). FTD with ubiquitin-positive inclusions (FTDU-17) was initially linked to the chromosome 17q21 region and has now been shown to be

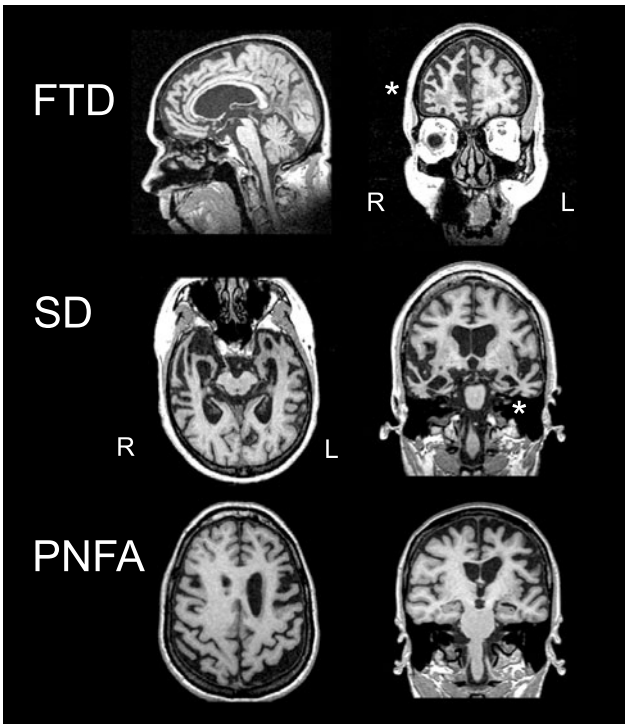

FIGURE 12–1. Magnetic resonance imaging findings in frontotemporal dementia (FTD).
FTD: Parasagittal and coronal images from T_1-weighted MRI scan. Note asymmetric right frontal atrophy on coronal image (*) and lack of significant atrophy posterior to frontal lobe on sagittal image.
Semantic dementia (SD): axial and coronal images; atrophy is most severe anteriorly and involves both medial and lateral temporal lobe structures (*).
Progressive nonfluent aphasa (PNFA): axial and coronal images show asymmetric left frontal atrophy with minimal temporal lobe involvement (*).

caused by loss of function mutations in the gene coding for progranulin, a growth factor involved in neuronal survival, tumorigenesis, and other processes (Baker et al. 2006; Cruts et al. 2006; van der Zee et al. 2007).

Treatment

No treatment has been shown to alter the course of FTD, but antidepressants, including selective serotonin reuptake inhibitors are useful in treating many of the behavioral symptoms (Huey et al. 2006). A serotonergic deficit is probably a component of FTD. Trazodone is the only medication for FTD to be studied in a double-blind, randomized controlled trial (Lebert et al. 2004). Trazodone is beneficial for a number of behavioral problems in FTD, including irritability, agitation, depressive symptoms, and eating disorders.

FTD does not entail a cholinergic deficit, and the use of cholinesterase inhibitors is controversial. In an open-label study, rivastigmine ameliorated behavioral problems in FTD (Moretti et al. 2004), but donepezil worsened behavioral symptoms in another study (Mendez et al. 2007). Other symptomatic treatments that have been tried are dopaminergic therapies for parkinsonism and language problems. A prospective trial of memantine for FTD is underway. No treatment for FTD is FDA approved. Clearly, more treatment studies of FTD are needed, especially randomized, controlled trials.

KEY POINTS

- Gradual personality change with impaired judgment in older adults is often because of FTD.
- FTD may be the most common cause of dementia for persons in their 50s and 60s.
- Patients with FTD may present with disorders of language expression or comprehension.

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CHAPTER 13

Traumatic Brain Injury

Erin D. Bigler, Ph.D.

The Centers for Disease Control and Prevention (CDC) (2007) estimates that 1.1 million emergency room visits, 235,000 hospitalizations, and 50,000 deaths occur each year as a result of a traumatic brain injury (TBI). The actual incidence of TBI may be even higher because many mild TBIs are never seen in the emergency room (Langlois et al. 2005). Thurman et al. (2007) estimate that more than 80,000 individuals become disabled from TBIs each year. As such, TBI represents a substantial source for neuropsychiatric morbidity and disability.

From a cognitive perspective, there are three likely proximal outcomes from having sustained a TBI: 1) recovered cognitive ability, with no demonstrable neuropsychological effect of the brain injury after a period of recuperation; 2) residual cognitive impairments, some sufficient to classify as a cognitive disorder, not otherwise specified (NOS), but not to the level meeting criteria for presence of a dementia; or 3) dementia due to head trauma. The focus of this chapter is on the last category. However, even in those who appear to recover fully from the proximal effects of TBI, the brain injury itself may represent a latent vulnerability factor only to be expressed later in life, increasing the likelihood of dementia decades after the acquired brain injury. Thus, a distal neuropathological sequelae in recovered TBI patients may be a latent pathological effect that during the aging process interacts with other environmental, constitutional, and genetic factors to be expressed later in life as a neuropsychiatric disorder associated with greater cognitive decline and earlier onset of frank dementia later in life because of the prior brain injury (Starkstein and Jorge 2005; Suhanov et al. 2006; van den Heuvel et al. 2007).

Of particular interest for the distal effects of TBI is that at the acute histopathological level TBI induces several pathological changes that also occur in age-related degenerative diseases like Alzheimer disease (DeKosky et al. 2007), which is discussed later in this chapter. Indeed, much has been written about TBI earlier in life being a substantial risk factor for dementia and other neuropsychiatric problems later in life (Gualtieri and Cox 1991; Hinkebein et al. 2003; Kiraly and Kiraly 2007; Lye and Shores 2000; Rao and Lyketsos 2002; Starkstein and Jorge 2005; Zhang and Sachdev 2003). This chapter addresses both of these issues, using the natural dichotomy of proximal-versus-distal effects of head injury leading to dementia.

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TABLE 13–1. Dementia due to head trauma

The essential feature of Dementia Due to Head Trauma is the presence of a dementia that is judged to be the direct pathophysiological consequence of head trauma. The degree and type of cognitive impairments or behavioral disturbances depend on the location and extent of the brain injury. Posttraumatic amnesia is frequently present, along with persisting memory impairment. A variety of other behavioral symptoms may be evident, with or without the presence of motor or sensory deficits. These symptoms include aphasia, attentional problems, irritability, anxiety, depression or affective lability, apathy, increased aggression, or other changes in personality. Alcohol or other Substance Intoxication is often present in individuals with acute head injuries, and concurrent Substance Abuse or Dependence may be present. Head injury occurs most often in young males and has been associated with risk-taking behaviors. When it occurs in the context of a single injury, Dementia Due to Head Trauma is usually nonprogressive, but repeated head injury (e.g., from boxing) may lead to a progressive dementia (so-called dementia pugilistica). A single head trauma that is followed by a progressive decline in cognitive function should raise the possibility of another superimposed process such as hydrocephalus or a Major Depressive Episode.

Source. From American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Copyright 2000, American Psychiatric Association. Used with permission.

When head injury is the *proximal* cause of dementia, the patient never returns to premorbid level of function after the initial brain injury and never recovers sufficiently to overcome or compensate for the substantial cognitive and behavioral residua from the brain injury. By the standards of the *Diagnostic and Statistical Manual, 4th Edition, Text Revision* (DSM-IV-TR) (American Psychiatric Association 2000), "Dementia Due to Head Trauma" (classification code 294.1, p. 148) can be diagnosed when the presence of dementia is judged to be a direct pathophysiological consequence of head trauma (see Table 13–1). It has been understood since the beginning of classification of neuropsychiatric disorders that a significant TBI can result in dementia (Koponen et al. 2002; McEvoy 1981), and it is now well established that presence of dementia due to head trauma is a common cause of acquired dementia (Leon-Carrion 2002; McMurtray et al. 2006; Starkstein and Jorge 2005). However, the majority of TBIs are in the mild-to-moderate range, and although cognitive impairments are commonplace, the level of impairment and behavioral deficits do not warrant a dementia due to head trauma diagnosis for the majority of head injuries. As outlined in Table 13–1, clear criteria have to be met before the dementia due to head trauma diagnosis is made, and because moderate-to-severe TBI occurs in only a minority of all TBI cases, it represents a less common diagnosis than a DSM-IV-TR cognitive disorder NOS classification (DSM-IV-TR code 294.9, p. 163) in those left with cognitive sequelae from a brain injury. Nevertheless, those left with some cognitive impairments following a TBI may represent a group most vulnerable to the long-term consequences of TBI earlier in life.

When head injury is a *distal* cause or factor in the development of dementia, the assumption is that the individual has experienced a relatively good, or what may even appear to be complete, recovery from the original brain injury; however, this head injury represents an adverse event creating various latent neuropathological vulnerabilities expressed only later in life (Bigler 2007c). Distal effects of TBI that eventually lead to dementia presupposes that the brain-injured individual sufficiently regained cognitive, behavioral, and psychosocial abilities following the TBI to return to independent living, being capable of typical vocational pursuits and family social function. Thus, it is only decades later that the ill effects of the prior brain injury and its role in the emergence of dementia occur.

In this chapter, I first discuss the proximal effects of TBI and how the diagnosis of dementia due to head trauma is made. The distal effects of TBI will then be discussed.

Proximal Effects of TBI: Dementia Due to Head Trauma

TBI that leads to dementia due to head trauma occurs when an individual has sustained a moderate-to-severe brain injury in which prior level of cognitive function is not regained and the general criteria for dementia are met. As outlined elsewhere in this text and by Holsinger et al. (2007), based on DSM-IV-TR criteria, "dementia is diag-

nosed when there are multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: agnosia, aphasia, apraxia, or a disturbance in executive functioning. The deficits that make up dementia can be diagnosed clinically. The deficits must be sufficient to cause functional impairment in home or work life and must represent a decline from previous functioning (p. 2392)." Because a distinct antecedent event is known in TBI-associated cognitive disorders, there is little doubt about the causal relationship of the head injury to the proper diagnosis of dementia due to head trauma when criteria are met (see Table 13–1). Three actual clinical cases will be described to demonstrate the proximal effects of TBI and the appropriate use of this dementia classification.

With regard to the level of cognitive impairment, in the most severe cases this can be documented during standard mental status examination, including screening psychometric tasks such as the Mini-Mental State Examination (MMSE) (Lorentz et al. 2002), in which scores less than 25 typically indicate significant cognitive impairment. In some cases more detailed neuropsychological measures (see Lezak et al. 2004) may be necessary. For example, the case presented in Figure 13–1 is from a patient who clearly met dementia due to head injury criteria. He had sustained a severe TBI as an adolescent, and although he had received extensive inpatient and outpatient treatment, he never recovered cognitive and praxic functions to live independently. When tested postinjury as a young adult, his overall intelligence quotient (IQ) standard score was 78. His MMSE score was 17. Preinjury school records reflected average academic performance with no history of learning or developmental disorder, and therefore it was assumed that no preinjury cognitive disorder was present. Before the injury he had never been diagnosed with a neuropsychiatric condition. Although IQ testing was not available prior to injury, academic and developmental history were described as "normal," and therefore it was assumed that premorbid IQ would have been in the "average" range, somewhere around a standard score of 100. More striking postinjury, however, was that the level of his memory impairment yielded standard scores consistently less than 60, demonstrating marked impairment in short-term memory. A severe constructional apraxia with an inability to copy simple forms was also evident (see Figure 13–1). Therefore the discrepancy in his postinjury-measured cognitive functioning represents a significant and distinct decline from premorbid levels and over a 5-year span of monitoring never changed significantly. As such, this patient met all criteria for DSM-IV-TR classification of dementia due to head trauma. One last distinction that needs to be made is that in cases of dementia due to head trauma, this diagnosis is made after a period of stable cognitive impairments. Unlike dementias associated with progressive degenerative diseases such as Alzheimer disease, dementia associated with head trauma is reflective of the stable cognitive deficits associated with a chronic and static encephalopathy.

Neuroimaging Findings and Their Utility in Diagnosis

Significant advancements in detecting TBI abnormalities have come from contemporary high-field magnetic resonance imaging (MRI) and functional neuroimaging techniques (Metting et al. 2007; Taber and Hurley 2007). Understanding the degree and extent of functional damage via methods of neuroimaging greatly assists the clinician in understanding the effects of TBI (Bigler 2005, 2007b).

Even the earliest computerized tomography (CT) studies, primitive by present-day standards, demonstrated that the extent of TBI-induced structural brain damage was linearly related to the severity of brain injury, and both were coarsely related to the degree of cognitive impairment (Cullum and Bigler 1986; Levin et al. 1981). This relationship is demonstrated nicely by the more recent study of Wilde et al. (2006), which examined the association between posttraumatic amnesia (PTA) and the development of cerebral atrophy. PTA is often used as a marker of initial injury severity, in which PTA of less than 30 minutes is considered mild, greater than 30 minutes but less than 24 hours is considered moderate, and 24 hours or greater is considered severe (Bigler 2008). Wilde et al. (2006) calculated that the odds of developing cerebral atrophy based on quantitative MRI increased by 6% with each day of PTA. In addition to greater amounts of cerebral atrophy, longer PTA is associated with worse functional outcome (Nakase-Richardson et al. 2007), in that the combination of longer PTA and greater amounts of cerebral atrophy are associated with the poorest TBI outcome (Bigler et al. 2006). Thus, for the clinician making decisions about injury severity and issues of dementia, markers of brain injury severity, including PTA, or length of coma as measured by presence of a low Glasgow Coma Score (GCS), directly relate to increased likelihood of trauma-induced cerebral atrophy, and presence of cerebral atrophy is associated with worse outcome from TBI and presence of dementia due to head trauma.

MRI studies of the brain can readily demonstrate clinically relevant TBI-related atrophy. For the case example described in Figure 13–1, the MRI findings of this patient as shown in Figure 13–2 demonstrate extensive structural damage to the entire brain but particularly in frontotemporal regions. This finding can be appreciated readily by

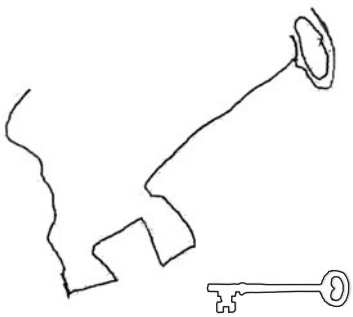

FIGURE 13–1. Apraxic attempt at drawing a key.
The patient whose neuroimaging studies are shown in Figure 13–2 displayed prominent constructional apraxia (inability to draw to command or copy simple figures) in his attempt to copy a simple line drawing of a key. This was likely a result of the loss of integrative cognitive control as a consequence of the diffuse brain injury, with particular deficits noted in the frontal regions bilaterally, and right parietal as shown in Figure 13–2.

viewing the reconstructed brain in three-dimensional views. Although not essential for making the diagnosis of dementia due to head trauma, in this patient, being able to visualize the scan in conjunction with the neuropsychological test performance as previously described (see Figure 13–1), along with knowing that his initial GCS was 3 and that he had weeks of coma and months of PTA, greatly aides in being confident in the dementia due to head trauma diagnosis.

As shown by the case in Figure 13–2, frontal and temporal lobes are particularly vulnerable to injury (Bigler 2007a). Also, the increased likelihood of frontotemporal damage always occurs amid the occurrence of diffuse injury (Bigler 2005, 2007b). Likewise, damage to frontotemporal systems from TBI carries with it a greater likelihood of cognitive impairment and disability (Wilde et al. 2005). There are multiple reasons for the increased likelihood for frontotemporal damage in head injury, including how the anterior and middle cranial fossa interface with the brain creating vulnerability sectors that increase the chance of contusions and/or deformation injuries to the brain (see Bigler 2007a). Because the medial temporal lobe, basal forebrain, and cholinergic systems of the brain are so commonly damaged in moderate-to-severe TBI (Arciniegas 2003; Salmond et al. 2005), damage to these regions represents another common connection between TBI and the development of dementia.

Progression of Atrophy From Day of Injury Until Stabilization

To understand fully the impact of TBI on brain structures and the degree of resultant cerebral atrophy, it is often clinically instructive to view the progression of cerebral damage from acute stages to chronic residuals. This is nicely shown in the case presented in Figure 13–3. The day-of-injury scan demonstrates multiple hemorrhagic lesions, intraventricular hemorrhage, and generalized edema. Despite these extensive abnormalities, the ventricular system can be well visualized, and it is readily apparent that, other than the acute brain pathology, the brain exhibited no congenital abnormalities, and the ventricular system was within normal limits for age at the time of injury. As such, even though the acute scan demonstrates prominent neuropathological changes, the otherwise intact features help the clinician establish baseline information for future comparison. Subsequent CT imaging clearly shows over time how ventricular dilation (hydrocephalus ex vacuo) can be readily appreciated where the ventricular expansion is a reflection of brain parenchyma volume loss (Bigler 2005, 2007b).

By viewing these scans in progression, it is obvious that a serious brain injury has occurred resulting in extensive cerebral atrophy, but the cerebral atrophy is essentially stable after a few months posttrauma. Given the severity of this TBI (GCS=3), extensive nature of the cerebral damage and its progression and then stabilization and mental status examination of impaired cognition (MMSE<10) 4 years postinjury when examined; this patient clearly meets criteria for dementia due to head trauma. Thus, starting with the day-of-injury scan, the degree of cerebral atrophy can be documented over time, typically within 6 months postinjury, and focal frontotemporal atrophy and/or significant generalized atrophy are the neuroimaging findings most likely to be associated with dementia due to head trauma.

Additional Factors That Contribute to Dementia Due to Head Trauma Diagnosis

Both animal models and human studies have demonstrated the vulnerability of the hippocampus in TBI (Bigler 2007a). In humans, this vulnerability of the medial temporal lobe and hippocampus is multifaceted in part because of their location in the middle cranial fossa (Carbonell and Grady 1999) but also to excitotoxic reactions that occur in traumatically injured hippocampal neurons (Geddes et al. 2003); diaschisis plays a role as well because hippocampal neurons have diverse afferent and efferent cortical connections (Wilde et al. 2007). Because the medial temporal cortex (and in particular the hippocampus) is so critical to all cognitive functions, damage to this region has a high likelihood for disrupting cognition, yet, even with extensive damage, the result may not be that the

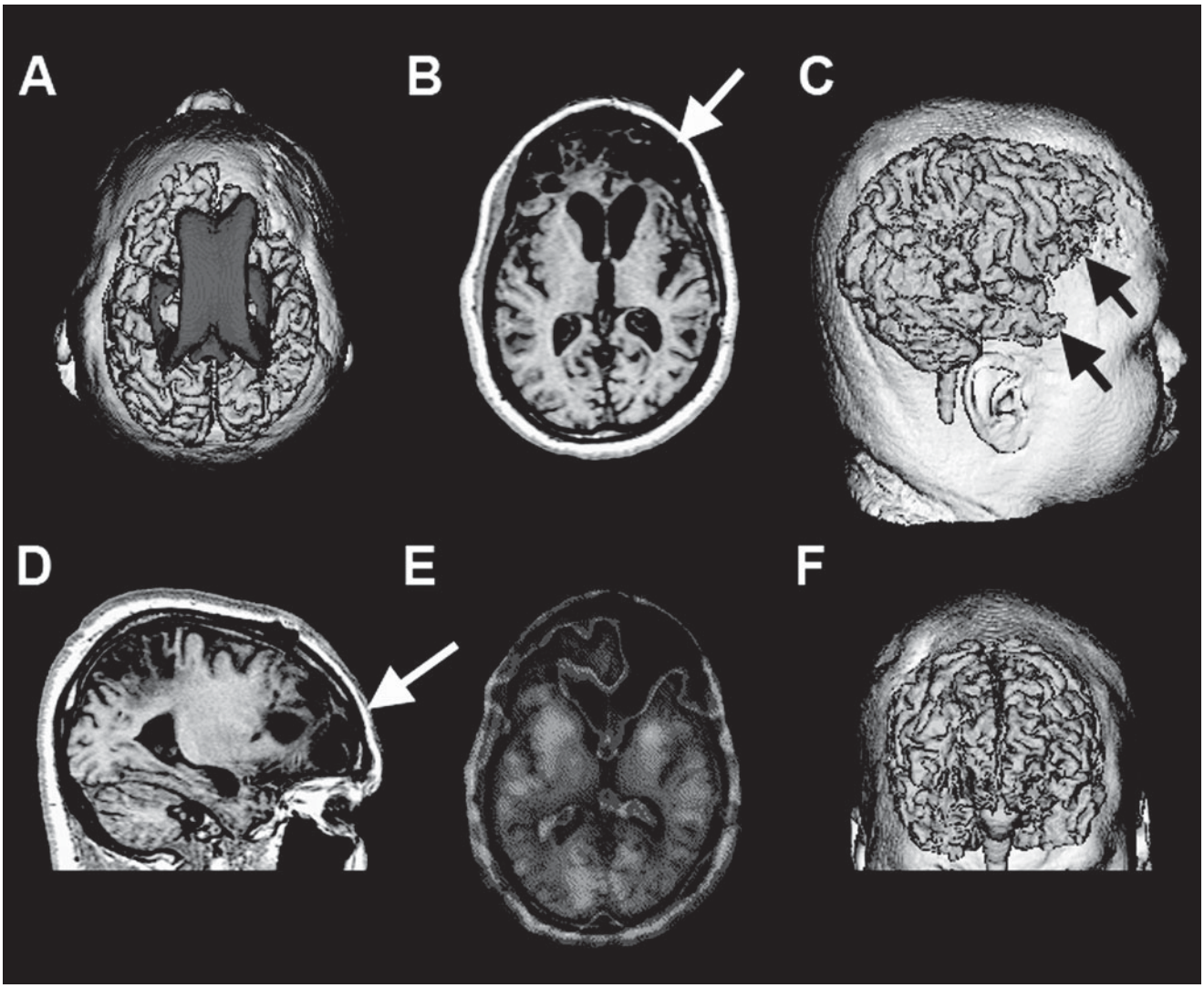

FIGURE 13–2. Neuroimaging in a case of dementia due to head trauma. *(See color plate 10)*
Neuroimaging studies for the subject discussed in Figure 13–1. *B* is an axial T_1-weighted magnetic resonance imaging (MRI) image showing extensive frontal damage (white arrow) as a result of the severe traumatic brain injury (TBI). *D* is a sagittal T_1-weighted image showing the extensive frontal (white arrow) pathology present in this patient. *A, B,* and *F* all represent three-dimensional (3-D) reconstructions of the MRI as to visualize the ventricle (shown in blue) in the dorsal view in *A,* and the extensive frontotemporal wasting (black arrows) in *C* and by viewing the bifrontal atrophy, particularly in the inferior frontal region in *F. E* is the view of single photon emission computed tomography (SPECT) findings at the same axial level as depicted in *B.* Note the extensive loss of frontal perfusion on the SPECT image. Lastly, note the generalized ventricular dilation (see *H* in Figure 13–4 for what a normal dorsal view should appear like). These imaging findings clearly demonstrate diffuse brain damage and generalized TBV loss, wherein the dementia due to head trauma diagnosis was straightforward to make given these neuroimaging findings, in conjunction with the history and neuropsychological assessment findings.

patient meets criteria for dementia due to head trauma, but only cognitive disorder, NOS, as shown in Figure 13–4. This adolescent patient sustained a severe TBI in a motor vehicle accident (GCS=3). The scan demonstrates clearly medial temporal lobe atrophy with prominent wasting of the hippocampus. Positron emission tomography imaging even confirmed reduced uptake throughout the medial temporal lobes bilaterally, yet neuropsychological studies demonstrated only mild memory impairment and related cognitive impairments. His MMSE was 26. Thus, despite these rather dramatic imaging findings and the presence of some cognitive sequelae from the TBI that certainly met criteria for cognitive disorder, NOS, the level of cognitive impairment was not to the degree to warrant dementia due to head trauma classification.

Wilde et al. (2007) also have shown that in comparison to all other brain structures the hippocampus shows the greatest atrophic changes in response to TBI. From this

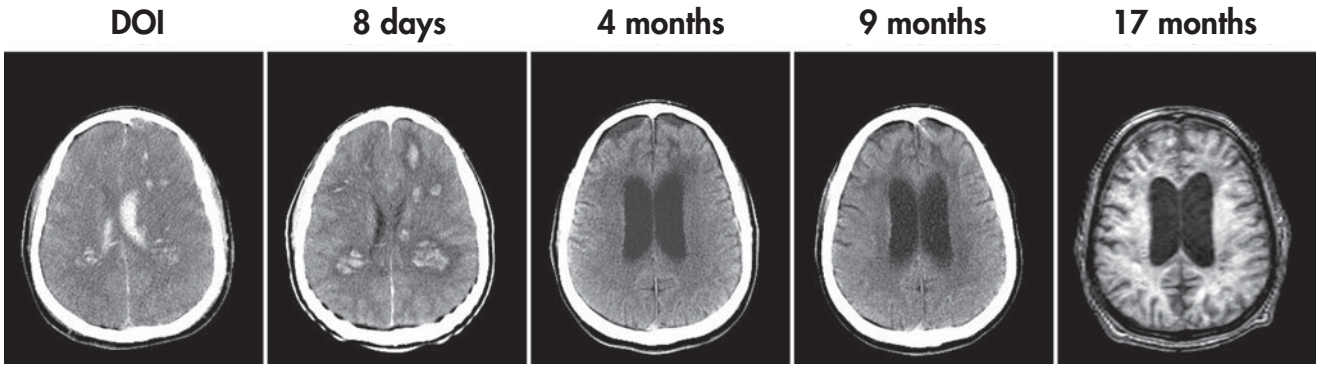

FIGURE 13–3. Progressive cerebral atrophy and ventricular dilation in case of dementia due to head trauma.
This patient sustained a severe traumatic brain injury (Glasgow Coma Score=3) with months of coma and persistent posttraumatic amnesia. Since regaining consciousness, his Mini-Mental State Exam score has been consistently below 10, and all of this represents profound impairments consistent with dementia due to head trauma. The sequence of imaging demonstrates the utility of tracking trauma over time so the clinician can best understand the extent of trauma-induced degenerative changes. The day-of-injury computed tomography scan demonstrates multiple intraparenchymal and intraventricular hemorrhagic lesions scattered throughout the brain, some of which "blossom" by 8 days postinjury. However, by 4 and 9 months postinjury ventricular dilation, as a sign of generalized brain volume loss, has pretty much reached its apex and shows little change thereafter, even in the magnetic resonance imaging (MRI) studies done 17 months postinjury (there is movement artifact in the MRI; that is why the images are fuzzy). Examining neuroimaging studies over the first few months postinjury is very instructive about the total amount of parenchymal damage.

and other research it can be concluded that there is likely hippocampal injury at some level in most cases of TBI (Harry and Lefebvre d'Hellencourt 2003). Also, it should not be overlooked that the hippocampus plays a role in emotional control and is potentially injured by stress-related hormones that are part of both the physical as well as emotional reaction to injury (Wolkowitz et al. 2007). The fact that there is a high incidence of neuropsychiatric sequelae, including depression, in TBI victims (Holsinger et al. 2002) and that such clinical findings may relate to reduced hippocampal volume (Jorge et al. 2007) underscores the multifaceted role that hippocampal damage may play in emotional and cognitive sequelae of TBI. Of particular interest is speculation that injury may disrupt neurogenesis that occurs in the hippocampus and that presence of amyloid may reduce the rate of neurogenesis (Morgan 2007). Thus, TBI-induced hippocampal damage can be linked to neuropsychiatric features of TBI. Presence of premorbid neuropsychiatric disorders may represent vulnerability factors for later expression of dementia (Starkstein and Jorge 2005) (discussed later in this chapter).

Speed of Processing Deficits in Traumatic Brain Injury

A rather universal sequelae from TBI, directly related to the severity of injury and persistence of neurobehavioral symptoms, is reduced speed of processing (Mathias and Wheaton 2007). There are two main neuropathological consequences of TBI that impair processing speed. First, any recovery from focal pathology likely occurs because of alternate, redundant, or adaptive pathways taking over function (Bach-Y-Rita 2003), and by the very nature of this adaptation this becomes a less direct way of processing, which increases response time. The other main factor is the selective vulnerability of white matter in TBI (Bramlett and Dietrich 2007), wherein diminished white matter integrity results in less efficient neural transmission. In aging, the extent of white matter pathology directly relates to speed of processing, and both are related to the clinical presentation of age-related mild cognitive impairment (MCI) and dementia (Burns et al. 2005).

Because diminished speed of processing is a natural consequence of aging that affects the ability to perform executive function (Jennings et al. 2007) and because alterations in processing speed mirror normal changes in white matter integrity with aging (Charlton et al. 2007), the older the individual at the time of injury, the less resilient the brain is to injury. As such, it should be no surprise that if TBI adds to the burden of white matter pathology that processing speed and age effects at the time of injury come together to produce greater cognitive deficits in older subjects who sustain a TBI (Deb and Burns 2007). These age-mediated effects also can be demonstrated in animal models (Shah et al. 2006), which reinforces the likelihood of increased vulnerability of white matter damage leading to TBI-related cognitive disorders, including dementia, in those who are older at the time of brain injury.

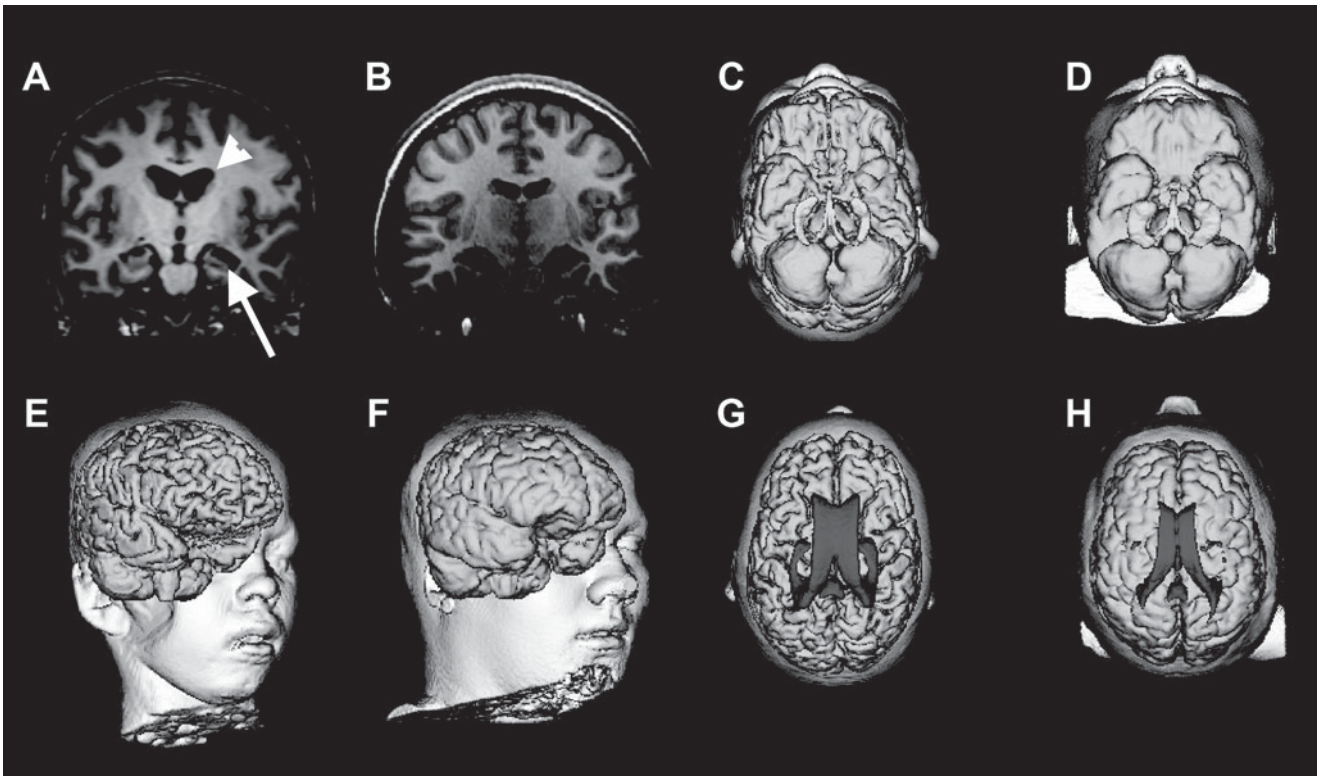

FIGURE 13–4. Hippocampal atrophy in head trauma. *(See color plate 11)*
The coronal T_1-weighted magnetic resonance imaging scan shown in *A* demonstrates pronounced hippocampal atrophy (arrow) along with dilated anterior horns of the lateral ventricular system (arrowhead) and prominence of cortical sulci, all indicators of generalized cerebral volume loss secondary to severe traumatic brain injury (TBI) as compared to an age-matched control subject in *B*. *E* (TBI patient) and *F* (age-matched control subject) three-dimensional (3-D) reconstructions nicely show the frontotemporal atrophy present in the TBI case *(E)* defined by the prominent sulci, whereas in the age-matched control subject sulci are very narrow in adolescence, rendering a more smooth, normal appearance to frontotemporal gyral patterns. This TBI patient *(C)* has profound hippocampal volume loss that can be readily appreciated in the 3-D reconstruction (ventral view) of the hippocampal formation and fornix, as shown in yellow, compared with the normal appearance of the hippocampus in the control *(D)*. 3-D dorsal view reconstruction of the surface anatomy shows generalized atrophy with prominent sulcal widening in the TBI patient *(G)* compared to the control subject *(H)* along with dilated ventricular system (shown in blue). These are indicators of generalized whole brain volume loss secondary to TBI-induced degeneration. However, this patient only meets criteria for cognitive disorder, not otherwise specified, and not dementia.

Genetics

Understanding genetic relationships of degenerative diseases and dementing illnesses has been an intense research focus for some time (Chai 2007; Foster 2007). Attention has now turned to the genetics of TBI outcome. For example, with the discovery of the association between the presence of the ε4 allele of the apolipoprotein E gene (APOE ε4) to Alzheimer disease, several TBI outcome studies have demonstrated that presence of the APOE ε4 genotype may be adverse to outcome following any type of acquired brain injury, including TBI (Alexander et al. 2007; Diaz-Arrastia and Baxter 2006; Isoniemi et al. 2006a, 2006b; Jordan 2007; Luukinen et al. 2005; Mauri et al. 2006; Mayeux et al. 1995; Smith et al. 2006). The genetics of dopamine regulation may also be very important to outcome following TBI (McAllister et al. 2006), and assuredly there are many other unknown genes at this time that participate in both protective and vulnerability factors associated with TBI, the aging process, and vulnerability for the development of dementia. The role that APOE ε4, or any other genetic factor, plays in recovery from TBI is complicated (Waters and Nicoll 2005) and beyond the scope of this review, and there are several negative reports or findings of minimal association (Han et al. 2007; Isoniemi et al. 2006b; Rapoport et al. 2008). Nonetheless, there are likely genetic factors that do represent vulnerability for poorer recovery from TBI and greater likelihood of residual and neurocognitive deficits that lead to the dementia due to head trauma classification.

Associated Vascular Effects

Traumatic axonal injury (TAI) is also associated with microvessel damage (Golding 2002; Ueda et al. 2006). Damage to the underlying cerebral microvasculature can, by itself, lead to dementia (Holsinger et al. 2007). The combination of TAI with microvessel damage can lead to widespread changes and impairment in cerebral integrity (Petrov and Rafols 2001). Of particular importance are the findings of Ueda et al. (2006), which show TBI-induced neurogenic changes in the vascular reactivity and local autoregulation of cerebrovasculature following a TBI. A particularly important feature of this dimension of injury is that localized cerebral perfusion may be disrupted, affecting the energy needs of neurons in regions where trauma-damaged blood vessels disrupt localized autoregulation. In this scenario, neurons may not be specifically damaged but nonetheless rendered functionally impaired because of diminished autoregulatory factors resulting specifically from the vascular injury, not necessarily the brain parenchymal injury. Thus, TBI-related cognitive impairments may be linked directly to trauma-induced vascular damage in addition to whatever direct effects occurred to neural tissue. It is likely that in those who meet criteria for dementia due to head trauma that associated vascular damage and/or vascular impairments contribute to the cognitive deficits.

Inflammatory Effects of Injury

Understanding inflammatory reactions in the brain has become an important part of identifying another dimension of neuropathological changes associated with injury, but it is also relevant to aging, disease, and dementia vulnerability (Candore et al. 2006). Initially, at the moment of first injury, the biomechanics of damage include stretching and shear-tensile forces on neural structures that physically damage the cell (Fitch and Silver 2008), inducing immediate physiological changes of increased membrane permeability to ions and other molecules that in turn may stimulate various inflammatory reactions (Laplaca et al. 2007; Marmarou 2007). These changes are widespread (Konsman et al. 2007; Lucas et al. 2006) and extend into the subacute or even into the more chronic phase of recovery from the injury (Pineda et al. 2007; Taylor et al. 2006) and, in turn, are likely very important in aging and the age-mediated effects of an injury (Cunningham et al. 2002). Whatever restoration occurs following a TBI, it does so through active neuron-glial cell repair mechanisms, in which the control of localized inflammatory reactions is key to maximum recovery (Floyd and Lyeth 2007). It should be mentioned again here that there are complex environment-stress responses to psychosocial factors that are likely at play as well, and these stress-mediated responses may also be influenced by local and global inflammatory reactions that, if sustained, may be adverse to optimum recovery. Anything that may increase a psychosocial stress response during recovery or adaptation to a TBI may have long-term adverse effects on cognition (Lee et al. 2007). TBI is a known psychosocial stressor (Prigatano et al. 2005), and therefore these potential environmental influences also must be considered when discussing inflammatory reactions. Although inflammatory reactions and their effect on recovery from injury as well as their relationship to brain health and aging are under intense investigation at this time, and likely play a role in cases of dementia due to head trauma, their exact role is not known at this time.

Stability of Dementia Due to Head Trauma: Living With a Brain Injury and Aging

Because the greatest likelihood of TBI occurs between the ages 15 and 30 years, the majority of those who are first diagnosed with dementia due to head trauma are young and have a lifetime ahead of them. To date there are no long-term studies that have examined whether there are predictable changes that occur with the aging process in those who have had a diagnosis of dementia due to head trauma at a young age. The assumption has been that the cognitive deficits that are present to the degree to warrant a dementia due to head trauma classification remain relatively stable over the lifetime of the individual, at least through the fifth decade of life. However, there is no research on this topic in which a group of patients with dementia due to head trauma have been followed prospectively for the remainder of their life. Himanen et al. (2006) examined 61 individuals who had sustained a TBI (combination of mild, moderate, and severe) earlier in life and followed for 30 years but did not specifically address those meeting dementia due to head trauma criteria. Nonetheless, as a group, cognitive impairments were present, as expected, at baseline and at age 30 years, at which cognitive decline with age during this time interval was described as being only "mild." Thus, the patterns of cognitive deficits appear to be stable in patients with chronic TBI, although age effects were present, resulting in age-related decline superimposed on the already impaired cognition.

To extrapolate these findings to those with dementia due to head trauma would suggest that unless other factors affect aging and cognition, those who receive this diagnosis early in life will likely be stable in function through at least midlife. As will be discussed later in this chapter, later in life there indeed may be a more accelerated degenerative pattern because of the prior head injury. Hinke-

bein et al. (2003) propose that the major problem with aging in someone with a history of TBI is that with age-related decline the neurocognitive deficits directly associated with TBI become more influential in altering the patient's cognitive status with age. In that sense, TBI plus aging in those who do not necessarily meet dementia due to head trauma criteria results in a mimicking of dementia symptomology but not necessarily dementia itself. For those who have dementia due to head trauma, although there may be a few decades of stable cognitive impairment, ultimately aging likely will have an adverse effect on that level of function, resulting in further declines.

Distal Effects of Head Trauma: Relationships to Neurodegenerative Changes Later in Life

In the last section, I discussed the direct and more immediate link between significant head trauma, cognitive impairment, and dementia. The key to that discussion is that after a brain injury the individual never returns to premorbid baseline and that even with the best recovery experienced, the individual still meets criteria for dementia classification. This section is very different in that the assumption is that the individual who has experienced a head trauma, regardless of its severity, has recovered to a level of cognitive functioning in which criteria for dementia due to head trauma are not met. Indeed, if the majority of TBIs occur in the mild range, and likewise if the majority of those with moderate to moderate-severe TBI have potential for good cognitive recovery (Wood and Rutterford 2006), then the vast majority of TBI patients would not meet criteria for a dementia. Most TBI patients in the mild-moderate range of TBI do recover sufficiently to resume some level of normal personal, vocational, and psychosocial functioning. However, from the previous discussion of TBI pathophysiology, neuropathological residuals likely are present in *all* individuals who have sustained a significant head injury, even with the best of recovery, and in whom the residual neuropathological effects have been compensated for in some adaptive fashion, and their ill effects are simply not expressed or may never be expressed during the postinjury years of good adaptation. In this scenario, the ill effects of the injury will be expressed only distally from the acquired injury, later in life, and only with the co-occurrence of yet unknown vulnerability factors or age itself. Candidate risk factors that potentially comingle with TBI and aging to produce dementia later in life are other health vulnerability factors such as other chronic illnesses (i.e., diabetes), cardiovascular disease, genetic predisposition (i.e., APOE ε4), additional head injuries, and other environmental factors, including drug and alcohol abuse. The review that follows examines the consequences during the aging process of having sustained a significant TBI earlier in life.

Traumatic Brain Injury as a Risk Factor for Alzheimer Disease and "Alzheimer's Pathology"

Epidemiological studies have raised the question of whether TBI earlier in life represents a risk factor for Alzheimer disease later in life (Jellinger 2004; Starkstein and Jorge 2005; Szczygielski et al. 2005; van den Heuvel et al. 2007). As early as 1985, Mortimer and colleagues described an association between head trauma early in life and the development of Alzheimer disease later in life, based on a case-controlled investigation. More recently a case-controlled design by Fleminger et al. (2003) provided a partial replication of the earlier findings by Mortimer et al. (1985). Guo et al. (2000), in one of the largest risk of head injury in the development of Alzheimer disease studies, examined 2,233 probands who met criteria for probable or definite Alzheimer disease and their 14,688 first-degree relatives. A relationship with prior head injury and the development of Alzheimer disease was observed. Despite these positive findings of an association, other studies have reported limited or no statistical associations of prior head injury with Alzheimer disease (see reviews by Jellinger 2004; Starkstein and Jorge 2005; Szczygielski et al. 2005; van den Heuvel et al. 2007).

Part of the problem of earlier research on this topic has been reliance on self-report of head injury. To counter that, Plassman et al. (2000) examined medical records of a cohort of military veterans to independently establish presence of head injury in the record. They gauged head injury severity as follows: 1) mild injury=loss of consciousness (LOC) or PTA less than 30 minutes, 2) moderate injury=LOC or PTA greater than 30 minutes but less than 24 hours and/or a skull fracture, and 3) severe injury=LOC or PTA greater than 24 hours. As shown in Figure 13–5, there was a relationship to injury severity and later diagnosis of dementia, including Alzheimer disease.

In a retrospective case-controlled study, Rosso et al. (2003) observed that in sporadic frontotemporal dementia (FTD) a history of head trauma had an odds ratio of 3.3 in those who had been diagnosed with FTD. These authors discussed the increased likelihood of frontotemporal damage from the original trauma to be associated with expression of FTD later in life.

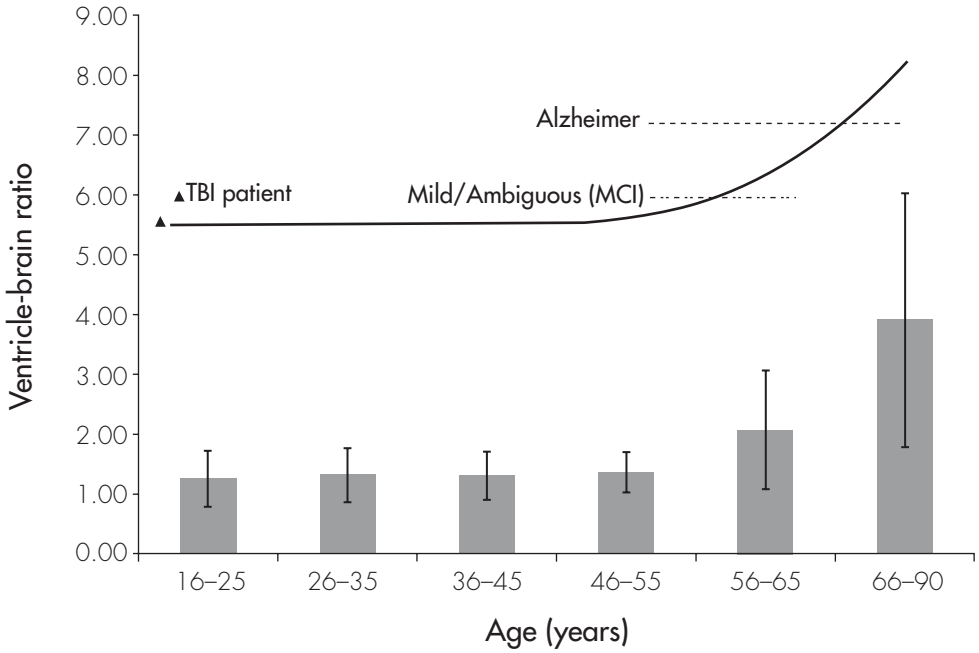

FIGURE 13–5. Normative ventricle-to-brain ratio (VBR) values from age 16 to 90 years.
Bar graph depicts mean value with vertical standard deviation bars. Note the general stability of VBR from age 16 to 55 years, but the normal aging process begins to be noticeably reflected thereafter as an increase in VBR. Again, the point needs to be emphasized that this represents "normal" or "typical" age-related ventricular dilation-brain volume loss. Moderate-to-severe traumatic brain injury (TBI) results in significant elevations of VBR reflective of generalized cerebral atrophy. The patient presented in Figure 13–4 had a VBR of approximately 5.55, markedly above the normative value for his age (see ▲ on graph). The graph is merely a reflection of the slope of VBR changes over age, with the starting point (▲) being the patient's elevated VBR at age 15 years when the imaging was performed. The horizontal lines reflect the VBR values for mild cognitive impairment (MCI) and Alzheimer disease subjects in a large population-based study that calculated VBR in an identical manner (see Bigler 2007c), wherein the MCI or Alzheimer disease classification came after age 65 years. Note that, using this overly simplistic heuristic, this young patient is already very near the degree of generalized cerebral atrophy as found in MCI and Alzheimer disease patients much later in life. In other words, his level of brain atrophy at age 15 years is like that of someone well beyond their seventh decade of life, yet he is only in his second. Examining global cerebral atrophy and ventricular enlargement with the aging process predicts those who deveop dementia (Kochunov et al. 2008; Nestor et al. 2008; Sluimer er al. 2008).
Source. Adapted from Bigler 2007c.

With the findings of the studies overviewed previously as well as topical reviews and meta-analytic analyses on this subject, a link is being established between prior head injury and the eventual risk of dementia. Obviously, this is an extremely complex issue, but the very nature of underlying neuropathology and selective vulnerability of certain brain regions, as discussed previously and to be revisited later in this chapter, likely represent the connection between TBI and later-in-life development of dementia.

Pathophysiological Basis of Prior Traumatic Brain Injury to Subsequent Dementia

Dementia pugilistica (punch-drunk syndrome), in which a boxer demonstrates increasing cognitive impairment associated with repetitive mild head injuries, was undoubtedly the first clinical syndrome to link earlier head trauma to development of dementia (Jordan 1992). As dementia pugilistica came under the scrutiny of postmortem histopathological analysis, these boxers were found to have neurofibrillary tangles and diffuse plaques of amyloid beta (Aβ) similar to lesions observed in those with Alzheimer disease (Roberts et al. 1990; Tokuda et al. 1991). This sparked a more general interest in TBI outside of boxer's encephalopathy, which was subsequently shown to be the case with TBI from road accidents, in which Graham et al. (1995) demonstrated that a single instance of brain trauma resulted in widespread deposition of Aβ (see also Brody et al. 2008). Simultaneous with these histopathological studies were the first large-scale studies attempting to make the link between head trauma and the development of dementia, in particular Alzheimer disease, as discussed previously.

It is now well established that immunohistochemistry staining for amyloid beta precursor protein (β-APP) is a sensitive method for detecting axonal damage in TBI (Hortobagyi et al. 2007). β-APP is a membrane glycoprotein produced in the cell body and is ubiquitous throughout the brain, where it plays a critical role in cell adhesion and endogenous neuroprotection in traumatic and other injuries (LeBlanc et al. 1992). However, as already mentioned, Aβ accumulation and plaque formation relate to Alzheimer disease, and this represents one of the potential links between prior TBI and subsequent development of Alzheimer disease (DeKosky et al. 2007; Gandy 2005; Lee et al. 2007; Mrak and Griffin 2005; Nakagawa et al. 1999; Olsson et al. 2004; Stone et al. 2002; Szczygielski et al. 2005). Additionally, Aβ burden likely relates to integrity of memory function in normal and pathological states (Morgan 2005), but because memory impairment is the commonality between TBI, aging, and dementia, these connections likely represent one of the major associations between acquired brain injury and subsequent development of dementia.

TAI, of which diffuse axonal injury is a subset (Smith et al. 2003), has been demonstrated to be widespread but particularly noted in the corpus callosum, the central white matter of the cerebral hemispheres, and the pons (see Hortobagyi et al. 2007; Xu et al. 2007), as well as the thalamus (Lifshitz et al. 2007). TAI occurs from primary axotomy associated with direct injury to the axon from shear-strain forces and from secondary injury effects, including ischemia, disrupted cytoarchitecture, associated metabolic injury, and Wallerian degeneration (Siman et al. 2004). Thus, not only is the overall Aβ burden in the brain elevated following TBI (DeKosky et al. 2007; Olsson et al. 2004; Raby et al. 1998), the white matter structural damage from diffuse axonal injury can be widespread and nonspecific (Bigler 2007b), disrupting the general connectivity of the brain (de la Plata et al. 2007; Farkas and Povlishock 2007; Newcombe et al. 2007). Indeed, Büki and Povlishock (2006) state that "all roads lead to disconnection," whether discussing acute, subacute, or chronic effects of TBI. The loss of white matter connectivity likely disrupts the brain and cognitive reserve during the aging process, increasing the likelihood of dementia later in life in those who have suffered a significant TBI.

Temporal Lobe and Alzheimer Disease Pathology

As shown by Hortobagyi et al. (2007), β-APP can be detected very shortly after brain injury, and Aβ deposition—along with a host of other acute neuropathological effects—induces inflammatory cytokine infiltrations with microglial activation and oxidative stress that relate to the ultimate effects of an acquired brain injury. Interestingly, these same factors are also considered important neuropathological antecedents in the development of dementia, including Alzheimer disease (Butterfield et al. 2007). In a most important histological study, Ikonomovic et al. (2004) examined excised tissue from TBI victims who underwent neurosurgical intervention for treatment of severe TBI. In each case (the patient required a craniotomy for this study), focus was placed on the excised temporal lobe tissue. They observed that the formation of immunohistochemically detectable extracellular Aβ deposits and other related degenerative changes occur early in the temporal lobe—within 2 hours after injury. Given the importance of the temporal lobe in cognitive functions, this association with Alzheimer disease–like degenerative changes that occur early in response to TBI, gives considerable credence to a link between prior head injury and development of dementia later in life. Furthermore, Swartz et al. (2006) examined temporal lobe tissue specimens from 21 patients operated on for posttraumatic epilepsy by partial temporal lobectomies and found that 94% of the specimens exhibited hippocampal neuronal loss. This finding simply underscores the vulnerability of the hippocampus and the fact that in the majority of patients with moderate-to-severe TBI there will be some loss of hippocampal neurons associated with the injury, despite the overall level of recovery.

Time Course of Atrophy in Traumatic Brain Injury

From the earliest of quantitative neuroimaging studies of aging, so-called normal progressive parenchymal volume loss of the brain has been associated with typical aging (Blatter et al. 1995; Raz and Rodrigue 2006). The issue in degenerative disorders is that the age-associated atrophic changes are surpassed by the degree of expected atrophy for age (Whitwell and Jack 2007). In such cases, degree of hippocampal and total brain volume (TBV) loss becomes predictive of those who cross over to dementia (Ridha et al. 2007). More than a decade ago, Blatter et al. (1997) demonstrated that in TBI normal age-related progression did not return to equilibrium until approximately 3 years postinjury and that there is on average a 50–100 cc TBV volume loss from moderate to severe TBI (Bigler 2001). However, most (60%–90% of total volume changes) of TBV loss in TBI occurs within 6 months of injury (see also Gale et al. 1995) (see also Figure 13–3). It was assumed that this volume loss occurred because of TAI, apoptosis, reduced synaptic complexity, and so on, during this recovery cycle. This has now become well documented in ani-

mal studies of TBI in which progressive changes appear to represent the brain's multifaceted attempt at neural repair and reintegration after injury (Bramlett and Dietrich 2007). There are well-documented animal studies that show active neuropathological changes over time can be detected during the year postinjury and even longer (Chen et al. 2004; Smith et al. 1997). It should come as little surprise that if the TBI is complicated by hypoxic-ischemic injury, which is often commonplace because of compromised pulmonary/airway or cardiac function secondary to trauma, that the progressive changes can be even worse than with just TBI alone (Truettner et al. 2007). Taken together, these injury factors mean global changes occur in the brain that can have deleterious consequences for the individual later in life.

As introduced previously, moderate-to-severe TBI results in significant reduction in TBV. So an interesting heuristic can be developed, as shown in Figure 13–5. Absolute TBV values are not necessarily that predictive of outcome in TBI, because TBV relates to body and head size differences along with sex differences. To overcome this variability in using TBV as a metric of brain health, a ventricle-to-brain ratio (VBR) is used in which total ventricular volume (TVV) is divided by TBV, which automatically corrects for head size differences (TTV/TBV × 100 reflecting a whole number). VBR, as a metric of generalized cerebral atrophy (Carmichael et al. 2007), remains relatively stable until the sixth decade of life, as shown in Figure 13–6, when age-related atrophic changes begin to be detected readily. VBR has been extensively studied in the aging process as well as TBI. In the case discussed in Figure 13–4, the patient had a severe TBI with marked generalized atrophic changes but did not meet clinical criteria for dementia; nonetheless, by superimposing the patient's VBR value and projecting it in comparison to known normative values, it is obvious that the patient's VBR crosses the mean age-related MCI and Alzheimer disease VBR values years before it would otherwise be expected. Similar findings have been reported for hippocampal volume loss (Bigler 2007c). Because whole brain and hippocampal volumetrics over time can be used to predict progression from asymptomatic, to symptomatic, to age-related MCI and on to actual Alzheimer disease (Devanand et al. 2007), if TBV is reduced or critical structures like the hippocampus have substantial volume loss as a result of TBI, volumes of these critical regions may cross pathological thresholds years to decades earlier than what would have normally occurred, leading to the distal or latent effects of TBI on the aging process.

As already introduced, in dementia pugilistica it has always been assumed that it was the repetitive nature of the blows to the head that related to the disorder (Jordan 2000; McCrory et al. 2007). There are indeed animal models of repetitive head injury that clearly demonstrate progressive pathology and experimental support that once the brain is injured it becomes more susceptible to repeated injury and that repeated injuries have a cumulative effect (Uryu et al. 2002; Weber 2007; Yoshiyama et al. 2005). While controversial, there are now several postmortem studies of professional athletes with repetitive head injuries that indicate a relationship between earlier injury, neuropsychiatric disorder, and dementia (Guskiewicz et al. 2007; Omalu et al. 2005, 2006). Similarly, there are high-field MRI studies demonstrating microstructure abnormalities in boxers, clearly indicating that subtle neuropathological changes are occurring in the brains of boxers even when they are not meeting clinical criteria for concussion (Chappell et al. 2006; L. Zhang et al. 2003, 2006). Likewise, cerebrospinal fluid markers of neuronal injury are seen in boxers, again in those not even meeting criteria for concussion (Zetterberg et al. 2006). Although there are no large-scale epidemiological studies on this topic at the time of this writing, there is considerable anecdotal information implicating head injury, including repetitive head injuries, acting as a trigger in initiating a cascade of changes that ultimately leads to dementia later in life (Kemp et al. 2005; Leung et al. 2006). It should be noted that in the short term that repeated sports concussions may not necessarily have a detectable cumulative effect (Iverson et al. 2006). However, the study by De Beaumont et al. (2007) is most interesting in regard to this issue. They examined college athletes with a history of single or multiple concussions using a visually evoked-response paradigm (oddball visual search), specifically measuring the third positive-wave component (P3). They found that in those who had sustained multiple concussions, significant amplitude suppression was observed. What is particularly important about this observation is that the multiconcussed and single concussed athletes did not differ on neuropsychological measures, implicating a latent effect that was not expressed in general behavior or cognition in those with multiple concussions at the time of assessment in their youth. Nonetheless, a subtle pathologic effect was present that was demonstrated objectively.

The Fate of Traumatic Brain Injury–Related Cognitive Disorder NOS

An area of concern with virtually no research at this time, but probably highly relevant to the issue of brain vulnerability over the life span once a brain injury has occurred, is what becomes of TBI-related cognitive disorder, NOS, in

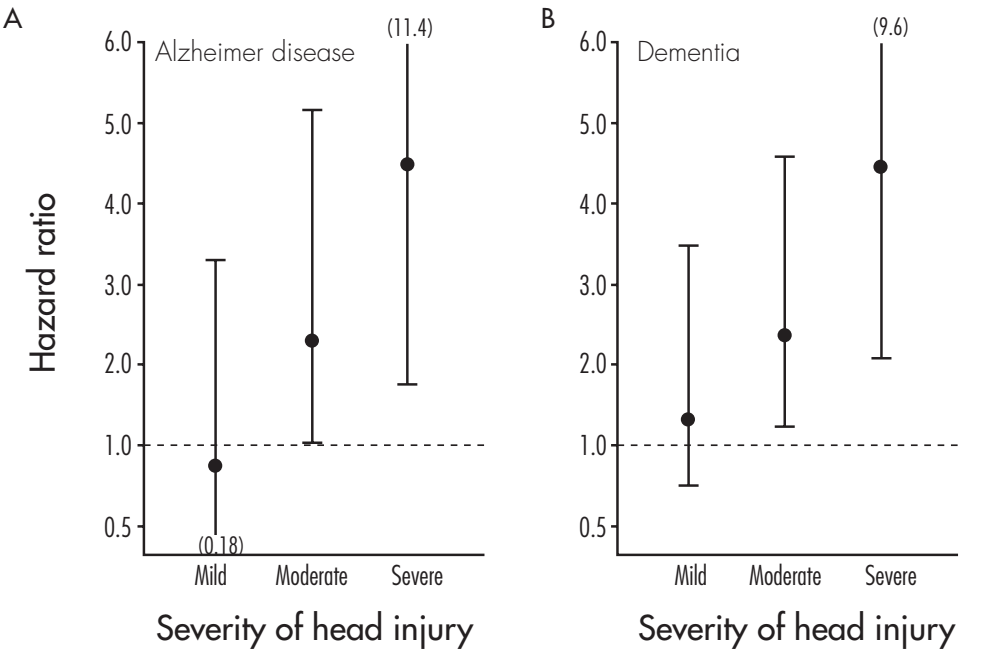

FIGURE 13–6. Hazard ratios in individuals with history of prior head trauma who develop dementia.
Plassman et al. (2000) calculated the hazard ratios of developing dementia later in life *(A)* and dementia in general *(B)* when traumatic brain injury (TBI) had occurred earlier in life. This graph clearly demonstrates a severity dose-response curve with increasing likelihood for dementia, including Alzheimer disease, when TBI occurs earlier in life. Bars represent 95% confidence intervals.
Source. Reprinted from Plassman BL, Havlik RJ, Steffens DC, et al.: "Documented Head Injury in Early Adulthood and Risk of Alzheimer's Disease and Other Dementias." *Neurology* 55:1158–1166, 2000. Copyright 2000 American Academy of Neurology. Used with permission.

those who have suffered a brain injury. Clearly, a significant number of TBI victims have residual mild cognitive deficits yet not to the degree that they meet criteria for dementia or that the cognitive deficits impair essential abilities for social and vocational independence. Many of these individuals have negative imaging by conventional standards and have adapted well to their brain injury, but nonetheless are assumed to have underlying subtle pathology (Cohen et al. 2007). MCI is the term most commonly used in dementia classification in which the aging patient has cognitive symptoms and subtle impairment on mental status examination but does not meet criteria for frank dementia (Petersen 2004). MCI-type problems are commonplace in TBI patients, so what does it mean to have mild symptoms of subtle cognitive impairment in the TBI patient as they age (Mauri et al. 2006)? We simply do not know the answer to this question, but because there are over 1.5 million TBIs annually, this is a question that needs answers.

Conclusion

Moderate to severe TBI can result in dementia due to head trauma. The more common diagnosis from TBI is cognitive disorder, NOS, with the assumption that residual cognitive impairments, even if they are not to the point to produce a proximal outcome of dementia, place that individual at increased risk for greater cognitive decline than typically would be the case during aging. Additionally, there are pathological features of TBI that have communality with those associated with aging and degenerative disease, and this creates a circumstance in which aging, genetics, and environmental and other health-related factors may interact with the prior head injury to increase the risk of dementia later in life. These latter effects may even occur in those who earlier in life appeared to fully recover from the brain injury.

KEY POINTS

- Moderate to severe TBI can result in dementia due to head trauma
- Dementia due to head trauma earlier in life is typically stable and nonprogressive, although this may change later in life because of the interaction of the aging *and* TBI along with other age-mediated vulnerability factors predisposing the TBI patient to a more rapid late-in-life decline.
- The proximal cause of dementia due to head trauma is likely a combination of diffuse injury along with more specific pathological changes in frontotemporolimbic structures.
- There is neuropathological overlap, including presence of Aβ associated with TBI and age-related degenerative disorders
- Head injury is a risk factor for dementia later in life that is dependent on the expression of other vulnerability factors.

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CHAPTER 14

Other Causes of Dementia

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The focus of this chapter is uncommon causes of dementia. The most common causes of dementia, Alzheimer disease, stroke, synucleinopathies, tauopathies, and traumatic brain injury, have been described in the preceding chapters. *Other dementias,* as they will be referred to here, account for less than 15% of cases of dementia (Larson et al. 1984). They can be divided into four categories for the sake of convenience: 1) diseases primarily affecting the central nervous system, 2) diseases primarily affecting organs outside the central nervous system (CNS), 3) diseases caused by exposure to substances (toxins), and 4) diseases caused by deficiency of essential substances (such as vitamin deficiency). Many of these conditions are arrestable or at least partly reversible, particularly if detected and managed early. Although *other dementias* are subdivided into distinct etiologies here, many patients have more than one cause of cognitive impairment.

Diseases Primarily Affecting the Central Nervous System

Genetic Disorders

Huntington Disease

Huntington disease is a progressive autosomal dominant neurodegenerative disease characterized by a hyperkinetic movement disorder and changes involving cognition and personality. Prevalence of the disease is 4–8 persons per 100,000, but five times as many individuals are at 50–50 risk of having inherited the genetic predisposition (Harper 1992). Most patients present in their fourth or fifth decades, although the range of onset can vary from juvenile to over age 65 years.

Huntington disease is caused by the expansion of a trinucleotide repeat mutation of cytosine-adenine-guanine (CAGn) in the 5'-translated region of the IT15 gene on chromosome 4p16.3 encoding the protein huntingtin (Huntington's Disease Collaborative Research Group 1993). The length of the CAG trinucleotide repeat mutation is inversely related to age at disease onset, accounting for at least 50% of the variance in onset age but can be modified by genetic factors in addition to the huntingtin gene (Duyao et al. 1993; Metzger et al. 2006; Wexler et al. 2004).

There is usually an affected parent. However, spontaneous mutations may occur. In addition to choreic hyperkinetic movements, dystonia and apraxia may be present. Walking may elicit the chorea in more subtle cases. Later, gait may become ataxic or dancelike. Oculomotor abnormalities include slow and hypometric saccades, saccadic pursuit, convergence paresis, and gaze impersistence. Orolingual apraxia is common. Parkinsonian features include decreased arm swing, bradykinesia, and dystonia. In the Westphal variant, more frequent in juvenile-onset disease, patients are hypokinetic and rigid. Cognitive and personality changes may precede the movement disorder and include obsessive and compulsive symptoms (Beglinger et al. 2007).

Patients and at-risk individuals can be tested for the triple CAG polymorphism. A polymorphism number greater than 39 represents definitive evidence of the disease. Age at onset of the movement disorder can be predicted using conditional probability tables (Brinkman et al. 1997; Langbehn et al. 2004). The disease may occur late or may not occur if there are 36–39 repeats. About 1% of patients suspected to have Huntington disease do not have CAGn expansion but have phenocopy syndromes (chorea, psychiatric and cognitive decline). These patients may have spinocerebellar ataxia type 17, Huntington disease-like syndrome 2, familial prion disease, or Friedreich ataxia. Other possibilities include dentatorubral-pallidoluysian atrophy, neurodegeneration with brain iron accumulation, neuroferritinopathy, or pantothenate-kinase-associated neurodegeneration (Wild and Tabrizi 2007).

Computed tomography or magnetic resonance imaging (MRI) scanning may show caudate atrophy. [^{18}F]Fluorodeoxyglucose positron emission tomography scanning can demonstrate striatal hypometabolism early on. In addition to atrophy of the striatum, particularly the caudate nuclei, there are reductions of γ-aminobutyric acid and acetylcholine levels and relative sparing of somatostatin-Y neurons in the striatum.

Treatment is symptomatic and palliative. In-depth information on management is provided in a physician's guide and through the Huntington's Disease Society of America (http://www.hdsa.org). It is important to attend to weight because these patients may use up to 5,000 kcal/day, and weight is inversely related to the amount of dyskinesias. Weighted wristbands can reduce the amplitude of dyskinesias. Speech therapy can improve communication and reduce risk of aspiration. Exercises and special equipment can improve mobility and comfort. For example a wheelchair cushion can help against slipping. Dopamine antagonists are the mainstay of drug treatment for the dyskinesias. Tetrabenazine or reserpine may be used. Common side effects include drowsiness, parkinsonism (an age-associated effect), depression, and akathisia (Kenney et al. 2007). Potentially neuroprotective therapies include the antibiotic minocycline, which inhibits caspase-1 and caspase-3 activity and is well tolerated at 100 mg bid. Other potentially neuroprotective therapies are glutamate release inhibitors (riluzole), glutamate receptor blockers (amantadine, memantine, lamotrigine), tetrabenazine, ubiquinone, creatine, ethyl eicosapentaenoic acid, and phenylbutyrate (Reynolds 2007). Genetic counseling and presymptomatic testing of at-risk relatives should be considered part of the management. Affected individuals are at high risk for suicide. Death occurs 10–20 years after onset from swallowing or breathing difficulty and their consequences.

Hepatolenticular Degeneration (Wilson Disease)

Wilson disease is an autosomal recessive disorder of copper metabolism. The disease may manifest in individuals between age 6 and 60 years but affects most individuals in the first two decades of life. Excess copper deposition results from the dysfunction of a copper-transporting P-type ATPase encoded on chromosome 13 (Huster et al. 2003). Copper transport into ceruloplasmin and subsequent excretion into bile is disrupted. Copper accumulates in and damages the liver, the basal ganglia of the brain, the kidneys, the cornea, and other tissues by inducing free-radical reactions and lipid peroxidation (Langner and Denk 2004). More than 200 mutations of the Wilson disease gene have been detected.

Family history is often negative because carriers do not manifest the disease. The disease may have different presentations even in the same family (Bitar et al. 1983). Positive family history is noted in 47% and consanguinity in 54% of cases (Taly et al. 2007). Presentations can include dystonia and the characteristic risus sardonicus, a facial dystonia mimicking a sardonic smile, from striatal deposition of copper. Vertical eye movements, in particular vertical pursuits, are impaired. Electro-oculogram abnormalities can be found in patients who do not yet exhibit lesions on MRI (Ingster-Moati et al. 2007). Other presentations include encephalopathy secondary to metabolic problems,

steatosis, cirrhosis, jaundice, and occasionally fulminant liver failure, kidney failure, or hemolytic anemia. Characteristic Kayser-Fleisher rings around the cornea are present in 100% of neurologic patients, 86% of hepatic patients, and 59% of presymptomatic patients. In one series, predominant neurologic features were as follows: parkinsonism, 62.3%; dystonia, 35.4%; cerebellar, 28%; pyramidal signs, 16%; chorea, 9%; athetosis, 2.2%; myoclonus, 3.4%; and behavioral abnormalities, 16% (Taly et al. 2007). Behavioral manifestations include disorders of affect, behavior, and personality and may include psychosis. Psychiatric symptoms occur during the early phase in approximately 50% of patients (Wichowicz et al. 2006). High levels of copper are found in blood, urine, and the liver; serum ceruloplasmin is low. Because of the high number of mutations, genetic testing is not practical. Computed tomography or MRI shows diffuse cerebral atrophy. The most common initial MRI abnormality among patients with Wilson disease is the occurrence of high T_1 signal intensity in the globus pallidus, putamen, and mesencephalon in association with hepatic dysfunction, or high T_2 signal intensity in the striatum among patients with neurologic symptoms (Magalhaes et al. 1994; Mochizuki et al. 1997).

The degree of brain pathology correlates with the amount of cerebral copper. Abnormal glial cells are present, and frequently there are gross or microcavitary changes in the putamina (Horoupian et al. 1988).

Treatment involves the use of metal chelators such as D-penicillamine or zinc sulphate. Potential future therapies include trientine and ammonium tetrathiomolybdate.

Chorea Acanthocytosis

Chorea acanthocytosis is a rare autosomal recessive disorder that is caused by a frame shift mutation on chromosome 9q21 encoding chorein (Ueno et al. 2001). It is manifested by chorea, dystonia and tics, psychiatric symptoms, and cognitive decline. Clinical features that distinguish it from Huntington disease are orofacial dystonia with tongue protrusion and biting of the tongue and lips. Additional features include seizures, distal amyotrophy, and neuropathy. Laboratory findings include characteristic red cell acanthocytes on peripheral blood smears and elevated serum creatine kinase.

Porphyria

The porphyrias are a group of inherited or acquired disorders of metabolism of the heme biosynthesis pathway. Each of the eight reactions in this pathway is catalyzed by a specific enzyme. The two major subtypes are hepatic or erythropoietic, depending on whether the metabolic step occurs in the liver or the bone marrow. The principal cause of central nervous system abnormalities is intermittent acute porphyria, which is often asymptomatic but may result in motor peripheral neuropathy, optic nerve atrophy, seizures, delirium, and coma. Porphyrias can cause a posterior leukoencephalopathy syndrome and cortical blindness. Porphyric encephalopathy is typically acute and intermittent. Neuroimaging may reveal multiple large contrast-enhancing subcortical white matter lesions that regress with glucose and hematin infusions. Diagnostic tests depend on the subtype of porphyria suspected. Plasma fluorescence scanning can detect porphyrins in the blood. Quantitative chromatography can measure porphyrins in urine, stool, or serum and can detect their levels by the microgram per liter. Enzyme assay of the heme synthetic pathway is particularly useful in acute intermittent porphyria. There is no consensus on treatment. Treatment of porphyria varies widely according to type of porphyria and to geographic location. Many drugs are unsafe in patients with porphyria. Of particular concern are hormonal contraceptives, local and general anesthetics, and anticonvulsants.

Neurodegeneration With Brain Iron Accumulation

Formerly known as Hallervorden-Spatz syndrome, neurodegeneration with brain iron accumulation is a heterogeneous group of disorders with different treatments. Common clinical manifestations are motor symptoms such as dystonia or parkinsonism, mental deterioration, retinitis pigmentosa, and iron accumulation in the brain. The differential diagnosis includes pantothenate kinase–associated neurodegeneration, which is an autosomal recessive disorder involving mutations in the pantothenate kinase 2 gene on chromosome 20p13, corticobasal degeneration, progressive supranuclear palsy, Parkinson disease, multiple system atrophy, giant axonal neuropathy, neuroaxonal dystrophy, Guam dementia, and HARP (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration) syndrome (Matarin et al. 2006; Zhou et al. 2001). Neuroimaging with MRI shows prominent T_1 signal hyperintensity in addition to the "eye of the tiger" sign on T_2 in the globus pallidum bilaterally. Susceptibility-weighted imaging, fast low-angle shot, and blood oxygen level–dependent MRI imaging techniques demonstrate mineral deposition in the globi pallidi better than conventional imaging (Vinod Desai et al. 2007).

Idiopathic Basal Ganglia Calcification

Idiopathic basal ganglia calcification is a rare autosomal dominant neurodegenerative disease that has clinical features that include parkinsonism, cognitive decline, and psychosis (Le Ber et al. 2007).

Mitochondrial Multisystem Disorders

A large number of mitochondrial disorders can produce neurological (muscle-specific symptoms, vision problems, or hearing deficits) and cognitive symptoms. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) can produce headaches and multiple small cerebral infarcts resulting in dementia. MRI reveals diffuse white matter disease (leukoaraiosis) and lacunar infarctions in nonhypertensive patients. Neuropsychological testing can reveal frontal-subcortical dysfunction. It can be challenging to diagnose because of the wide range of notch 3 mutations that can cause disease, but a new immunohistochemical technique using a skin biopsy sample appears to be highly sensitive and specific. Granular osmiophilic material within the basement membrane of vascular smooth muscle cells, as demonstrated on electron microscopy, is pathognomonic (Ishiko et al. 2005). In a landmark Icelandic study, linkage was established between stroke and a locus on chromosome 5q12 designated STRK1 (Meschia and Worrall 2004). The pathology is believed to be secondary to gradual destruction of vascular smooth muscle cells of arterioles leading to progressive wall thickening and fibrosis and luminal narrowing. Resultant lacunar infarcts have a predilection for the basal ganglia and frontotemporal white matter.

Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) can produce similar symptoms, absent infarcts. In a series of 22 patients with chronic progressive external ophthalmoplegia (Kearns-Sayre syndrome), neuropsychological testing did not reveal general intellectual decline or dementia but provided evidence of specific focal neuropsychological deficits, suggesting particular impairment of visuospatial perception associated to parieto-occipital lobes and executive deficits linked to the prefrontal cortex (Bosbach et al. 2003).

Neuronal Ceroid Lipofuscinosis

Neuronal ceroid lipofuscinosis is an autosomal recessive lysosomal storage disorder that can affect people at different ages. Clinical characteristics include progressive loss of vision, seizures, and loss of cognitive and motor functions, leading to premature demise. The juvenile form (Batten disease, Spielmeyer-Vogt-Sjogren disease, CLN3) is caused by mutations of the CLN3 gene, which encodes a hydrophobic transmembrane protein and which localizes to membrane lipid rafts in lysosomes, endosomes, synaptosomes, and cell membrane (Rakheja et al. 2007).

Leukodystrophies

Leukodystrophies are a group of degenerative diseases that primarily involve disturbances in the synthesis or catabolism of myelin. Metachromatic leukodystrophy results from a disorder of catabolism of sulphatides, whereas Krabbe disease results from a disorder of catabolism of galactocerebrosides and Pelizaeus-Merzbacher disease from abnormal synthesis of proteolipid protein. In Canavan disease, there is accumulation of acetyl aspartic acid. Common clinical features include neurological deterioration following a period of normal development, predominant involvement of motor function at least initially, and absence of convulsions or myoclonus. MRI shows changes in density or signal from central white matter (Aicardi 1993). Treatment is symptomatic. Bone marrow transplantation may stabilize the disease (Gorg et al. 2007); gene therapy trials show promise (Capotondo et al. 2007).

X-linked adrenoleukodystrophy is an X-linked peroxisomal disease associated with accumulation of the very long chain fatty acids hexacosanoic acid and tetracosanoic acid in different tissues and biological fluids. Many carriers are asymptomatic. Clinical manifestations in symptomatic patients include signs of progressive brain and peripheral demyelination and adrenal cortical insufficiency (Sutovsky et al. 2007).

Ataxia with vitamin E deficiency may result from mutations in α-tocopherol transfer protein (α-TTP). Transfer of absorbed vitamin E to a circulating lipoprotein is controlled by α-TTP, a 278 amino acid protein encoded on chromosome 8 (Copp et al. 1999).

Disorders With Unknown Etiology

Normal Pressure Hydrocephalus

The prevalence of normal pressure hydrocephalus (NPH) is unknown, but it is rare at best. In a review of the incidence of nondegenerative and nonvascular dementia spanning 5 years in Rochester, Minnesota, 560 incident cases of dementia were found. None was attributable to this disorder (Knopman et al. 2006). The classical clinical diagnostic triad involves gait disturbance, incontinence, and cognitive impairment in temporal sequence (Hakim and Adams 1965). Unfortunately, this triad is seen in a number of neurodegenerative disorders including some presentations of frontotemporal dementia, multiple-system atrophy, Parkinson disease, and dementia with Lewy bodies. These diseases also may share ventricular enlargement disproportionate to the level of cortical atrophy or to sulcal enlargement noted on neuroimaging. Other supportive findings on MRI include periventricular hyperintensity consistent with transependymal flow of cerebrospinal fluid (CSF), prominent flow void in the aqueduct and third ventricle (jet sign), rounding of the frontal horns, and elevation of the corpus callosum. Signifi-

cant improvement in gait immediately after high-volume (30 mL) lumbar puncture is strongly suggestive. The best method for diagnosis is intraventricular pressure monitoring.

One study group recommended classifying NPH into two major categories, idiopathic NPH and secondary NPH, and developed new evidence-based guidelines (Marmarou et al. 2005). The latest guidelines recommend that idiopathic NPH be classified into probable, possible, and unlikely categories based on history, imaging, and clinical criteria (Relkin et al. 2005). It will be important to follow suspected cases of idiopathic NPH prospectively and to document symptoms and response to treatment, followed by autopsy verification in order to validate guidelines for diagnosis and treatment in the future. Treatment involves implantation of a ventricular shunt to the peritoneum or the atrium. The shunt has to be programmable for different pressures to minimize risk of intracranial bleed secondary to stretching of bridging veins. Shunt complications occur in as many as 40% of cases. In cases of cognitive impairment or with concomitant cerebrovascular disease, prognosis for cognitive recovery after shunting is poor.

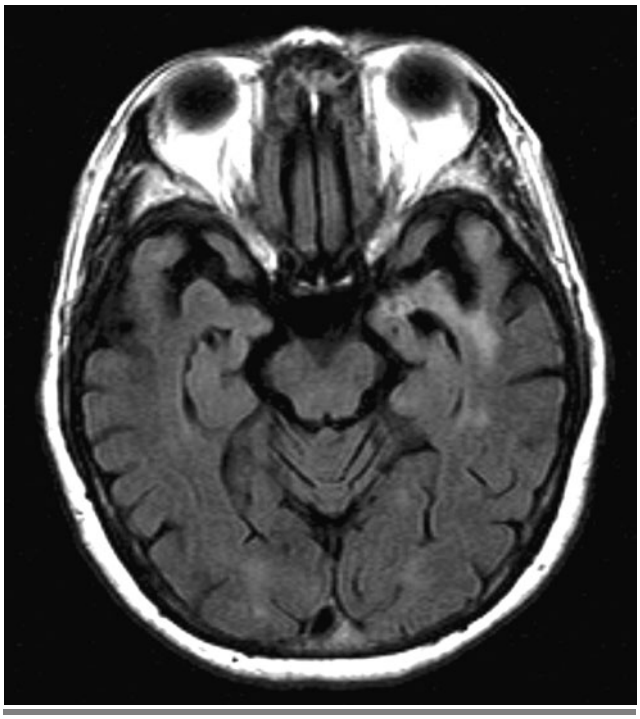

FIGURE 14–1. Magnetic resonance imaging fluid attenuation recovery demonstrating increased signal in the anterior left temporal lobe demonstrating secondary gliosis in a patient previously treated for herpetic encephalitis.

Infections of the Central Nervous System

Encephalitis

Most cases of encephalitis do not have an identifiable etiology. Only 16% of 1,570 patients enrolled in the California Encephalitis Project between 1998 and 2005 had identifiable causes. Sixty-nine percent of these agents were viral; 20%, bacterial; 7%, prion; 3%, parasitic; and 1%, fungal. An additional 13% had a suspected etiology, 8% were noninfectious, and the remaining 63% were unidentified (Glaser et al. 2006).

Herpes simplex virus encephalitis causes acute fever and altered behavior. Because this infection may produce lasting neurocognitive deficits, early recognition and management is very important. The virus has a predilection for the limbic system. Neuropsychiatric manifestations include anterograde amnesia, retrograde amnesia (Damasio et al. 1985), category-specific impairment of semantic memory (Lowe et al. 2005), and various kinds of aphasia. MRI reveals increased T_2/Fluid Attenuation Recovery (FLAIR) signal in the limbic areas (Figure 14–1). Diagnosis is by detection of virus in CSF by the polymerase chain reaction or by brain biopsy. Therapy is acyclovir 30 mg/kg/day. Untreated, morbidity and mortality are high.

The herpes zoster virus rarely produces encephalitis. Symptoms can include apathy, iridocyclitis, Korsakoff syndrome, paresis, and diplopia. Pilleri et al. (1981) reported an autopsy-confirmed case of thalamic encephalitis involving the anterior ventral, medial, and centrum medianum of the thalamus.

Subacute sclerosing panencephalitis is a delayed manifestation of measles infection. It typically occurs 7–10 years after infection but may occur as late as the fifth decade of life. Incidence has decreased substantially because of widespread vaccination against measles. Patients present with a decline in cognitive performance, behavioral changes, headache, myoclonic jerks, and possibly seizures. CSF has inflammatory features and a high IgG level. There is no definitive treatment, but intrathecal interferon alpha-2 with or without inosine pranobex (an antiviral immunomodulatory agent) has been used.

At autopsy, inflammatory infiltrates are seen around vessels with neuronal destruction and reactive gliosis. The white matter may be firmer than normal. Active viral particles are absent, unlike acute measles encephalitis.

Prion diseases are invariably fatal neurodegenerative disorders of the central nervous system responsible for transmissible spongiform encephalopathies in animals and humans. The normal cellular form of encoded prion protein (PrPc) undergoes a conformational change to an abnormal isoform, PrPsc. In humans, this conversion can

result in Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker disease, familial and sporadic fatal insomnia, and kuru. Most cases are sporadic, whereas about 15% are inherited and associated with mutations in the PrP gene, and a few cases are acquired through exposure to infected material. The latter group includes iatrogenic CJD, kuru, and variant CJD in humans. Prion diseases occur at a rate of about 1 per million per year with predilection for individuals age 55–65 years. Variant CJD tends to affect young individuals, averaging age 27 years. Incubation periods are long (years), but survival from first symptom is brief, 6 months for sporadic CJD and 15 months for variant CJD. Most cases occur in homozygotes at codon 129 of PRNP, in which either methionine or valine may be encoded. They include a large number of mutations and a wide spectrum of clinical and histopathological phenotypes. Dementia, ataxia, and psychiatric symptoms are present in all cases, and extrapyramidal symptoms in 88%. Increased T_2-weighted MRI signal is seen in the basal ganglia in 90% and in the thalamus in 88% of cases. CSF tau protein is elevated in 83% and protein 14–3–3 is positive in 76%. The electroencephalogram (EEG) periodic sharp wave complexes often associated with CJD were seen in only 2 of 26 patients (Krasnianski et al. 2006)

Diagnosis can be difficult and requires brain tissue for definite confirmation. The typical picture is one of rapidly progressive cognitive decline and behavioral change often accompanied with gait disturbance and myoclonic jerks. However, up to two-thirds of patients may present with atypical features such as fatigue and wasting, focal neurologic symptoms suggesting stroke, rigidity, and fasciculations, suggesting amyotrophic lateral sclerosis, or other neurologic syndromes. Clinical variants include occipital, ataxic, extrapyramidal, amyotrophic, frontopyramidal, and panencephalopathic. As noted above, the characteristic electroencephalographic biphasic or triphasic synchronized sharp-wave complexes are not often present. Presence of 14–3–3 protein, neuron-specific enolase, and S-100b protein in the cerebrospinal fluid are all highly suggestive but not specific. MRI may show multifocal areas of reduced diffusion involving the basal ganglia as well as the cortical mantle throughout both hemispheres and the cerebral cortex on T_2-weighted and diffusion-weighted images. Combining CSF total tau protein and MRI findings can identify 98% of early cases (Satoh et al. 2007; Zeidler and Green 2004).

Treatment is symptomatic and supportive. Several new approaches to therapy are under investigation. Classes of compounds under study include polysulfonated, polyanionic, and polycationic substances, amyloidotrophic intercalators, polyene antibiotics, tetracyclines, cyclic tetrapyrrols, polyamines, anthracyclines, acridines/bisacridines, designer peptides, RNA aptamers, tyrosine kinase inhibitors, and monoclonal antibodies (Féraudet et al. 2005; Ludewigs et al. 2007). A major hurdle for potential compounds is transport across the blood-brain barrier. Quinacrine and doxycycline are in clinical trials in the United States and in Italy and Germany, respectively (National Institutes of Health 2007; NeuroPrion 2006).

Human immunodeficiency virus (HIV)

HIV/AIDS currently is the most common cause of dementia in persons under age 40 years. Over 33 million persons are infected with HIV worldwide (UNAIDS 2007 statistics). This is a drop from the peak in the late 1990s. However, worldwide incidence is at an astounding 2.5 million per year. The HIV virus causes immunosuppression by infecting CD4+ t-lymphocytes. Disease stage is associated with reduction in CD4+ cells (>500 CD4+ cells/mL=asymptomatic, between 201–500 cells/mL are associated with constitutional symptoms, and <200 cells/mL is considered full-blown AIDS) (Centers for Disease Control 1993).

AIDS dementia was first described by Navia et al. (1986) with emphasis on the behavioral and motor aspects of the disorder. Although many AIDS patients developed dementia secondary to complications of HIV, some were noted to have cognitive impairment without evidence of secondary infections or malignancies. Since then, the American Academy of Neurology has developed criteria for this disorder (Working Group of the American Academy of Neurology AIDS Task Force 1991). Mild cognitive impairments associated with HIV may occur without frank dementia in up to 35% of otherwise asymptomatic individuals (Selnes and Miller 1992). Symptoms include forgetfulness, decreased attention/concentration, slowed thinking, and mild tremor. Patients report that they cannot retain information, such as when reading a book, or remember recent events. On neuropsychological testing, reduction in psychomotor speed is a prominent feature. Treatment of HIV with antiretroviral therapy can control the disease for many years and eliminate the occurrence of HIV-associated dementia.

Dementia or cognitive impairment secondary to complications of HIV may be caused by opportunistic infections or malignancies, such as CNS lymphoma. Potential secondary infections include cytomegalovirus encephalitis, toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, herpes simplex encephalitis, varicella zoster encephalitis, Epstein-Barr virus encephalitis, candida albicans microabscesses, aspergillus infection, amebic infections, neurosyphilis, and infection with atypical mycobacteria (Offiah and Turnbull 2006).

These can usually be ascertained by neuroimaging and CSF analysis for cells and titers.

Other infections

Hepatitis C virus (HCV) infection is common, affecting up to 2% of the world's population. Testing blood donors for HCV has dramatically reduced prevalence of infection. Rate of comorbid infection with HCV in patients with HIV is high (30%) and higher in intravenous drug users (60%–90%). Up to 20% of chronically HCV-infected patients may develop cirrhosis over a 20-year period and possibly cirrhosis-associated encephalopathy. However, up to one-third of people with chronic HCV experience cognitive impairment in the absence of cirrhosis (Perry et al. 2008). Early symptoms include fatigue, malaise, weakness, anorexia, and, occasionally, jaundice. Some persons complain of problems with attending to and recalling everyday information. This is most consistent with frontal-subcortical dysfunction and similar to that in patients with HIV. Interferon alpha is the primary antiviral therapy.

West Nile virus is transmitted by mosquitoes from birds to humans. It spread throughout the United States in the 1990s. The incubation period is between 3 and 14 days. About one in 150 infected persons will develop severe illness. Clinical manifestations of infection can mimic many neurological syndromes. Symptoms can include high fever, headache, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, vision loss, numbness, and paralysis. These symptoms may last several weeks, and neurological effects may be permanent (Centers for Disease Control and Prevention 2006). EEG findings are nonspecific and consistent with an encephalopathic pattern. Moderate to severe generalized slowing is present, and triphasic waves may appear. Treatment is supportive. Efforts at controlling the disease involve eliminating mosquito breeding sites and limiting exposure to mosquitoes.

Syphilis has become rare in settings outside of HIV. Infection with *Treponema pallidum* passes through three clinical stages. In primary syphilis, a chancre develops at the site of contact. Secondary syphilis occurs 6–8 weeks later, manifested by constitutional symptoms, a generalized lymphadenitis, and a mucocutaneous rash over the palms, soles, face, or scalp. After an asymptomatic latent stage that may last many years, a third of patients may develop tertiary syphilis (neurosyphilis). This typically occurs in the fourth and fifth decades of life. A patient may present with any combination of delirium, dementia, other neuropsychiatric conditions, stroke, spinal cord disease, and/or seizures. Tabes dorsalis has become uncommon (Timmermans and Carr 2004). CSF may show elevated protein and cell count. CSF-Venereal Disease Research Laboratory (VDRL) test is positive, with titers greater than 1:8 in about 77% of cases. When suspected, the CSF fluorescent treponemal antibody absorption (FTA-ABS) test can be performed. Neuroimaging shows cerebral atrophy. MRI may show meningeal enhancement. Treatment is with 20 million units/day of penicillin G for 14 days. The rate of residual symptoms can be high.

Lyme disease is caused by infection with *Borrelia burgdorferi* and transmitted by the bite of ixodid ticks. It may have a wide variety of clinical manifestations. Typically, there is an expanding bull's-eye rash at the site of the bite. This may be followed some months later by cardiac and neurologic symptoms, typically radiculitis or neuropathy, particularly involving the facial nerve. A minority of patients may develop arthritic or dermatologic symptoms years later. Rarely, encephalomyelitis and encephalopathy occur. Potential neuropsychiatric manifestations include virtually every psychiatric syndrome (Fallon and Nields 1994). Diagnosis is with a positive CSF polymerase chain reaction test. Various antibiotic regimens have been tried, but treatment of late manifestations with antibiotics may lead to only a partial response. Prolonged (14–30 days) parenteral cephalosporin treatment is preferred.

Fungal meningoencephalitis occurs mostly in HIV-positive and other immunocompromised patients, the more common culprits are *Cryptococcus neoformans,* coccidoidomycosis, histoplasmosis, blastomycosis, *Aspergillus,* and *Candida* species. Rare infections may occur from *Nocardia, Actinomyces, Paracoccidioides, Cladosporium, Allescheria, Cephalosporium,* and *Sporothrix.*

Diseases Primarily Affecting an Organ Outside the Central Nervous System

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic neurological disease that can cause both physical and mental disability. The triggers are unknown, but there is a genetic component that may predispose a particular individual to the disease. It is estimated that 400,000 people in the United States have MS (National Multiple Sclerosis Society 2008). At least half of persons afflicted by MS will become cognitively impaired (Bobholz and Rao 2003).

Cognitive profiles and the severity of cognitive deficits vary depending on the subtype of MS. Huijbregts et al. (2004) found that the most severe cognitive deficits occurred in subjects with secondary progressive MS, fol-

lowed by subjects with primary progressive MS, and then people with relapsing remitting MS. Denney et al. (2004) found that subjects with relapsing remitting MS did more poorly on measures requiring speed as compared with subjects with primary progressive MS. Severe dementia is uncommon but may occur in 20%–30% of cognitively impaired people with MS (Schulz et al. 2006).

Cognitive impairment may occur at any time during the disease. Schulz et al. (2006) found cognitive dysfunction within 24 months of diagnosis. Cognitive dysfunction occurs in men more than women (Savettieri et al. 2004), and early cognitive dysfunction may herald a poorer prognosis (Kujala et al. 1997).

The most common cognitive impairments are impaired learning and memory, slowed information processing, and impaired attention. Problems with spatial processing and executive dysfunction may also be seen less commonly (Medical Advisory Board of the National Multiple Sclerosis Society 2006). The feature most commonly associated with MS is slowed information processing (Feinstein 2007). Language typically is preserved (Schulz et al. 2006). Intelligence testing, in aggregate, tends to show some slight decline over time (Rao 1986).

Memory impairment is found in up to 60% of patients (Brassington and Marsh 1998). MS patients tend to need more time to learn a set of given information and are more susceptible to interference than control subjects. The pattern most commonly seen is that of retrieval failure. Recognition is usually intact. Memory impairment has been seen even in early stages of MS with little physical disability (Rao 1986).

Delayed processing speed is a principal feature of cognitive impairment in MS. Executive dysfunction may be seen in one-third of patients, even in the absence of frontal lobe plaques (Feinstein 2007). MS patients tend to perseverate on tasks of conceptual reasoning (Rao 1986; Schulz et al. 2006), and difficulties with concept analysis and abstract problem solving may be seen. Less common are impairments in visuospatial processing and language. Visuospatial difficulties such as facial recognition or visual organization may be experienced in some form by up to 20% of MS patients (Feinstein 2007). Although articulation is frequently affected, language is not usually affected.

The natural history of cognitive changes in people with MS is highly variable. Kujala et al. (1997) found that subjects who were initially cognitively normal remained so throughout a 3-year follow-up period, but those subjects who were cognitively impaired at the start continued to show decline. Piras et al. (2003) followed 12 patients over 8.5 years and found that their neuropsychological performances were stable. Amato et al. (2001) followed 110 subjects (45 with a recent diagnosis of MS and 65 control subjects) for 10 years and found that a little over half of the patients with MS were cognitively impaired, an increase from 25% with cognitive impairment at initial testing. Recall and abstract reasoning commonly were involved at first, followed by changes seen in linguistic abilities and attention. Schwid et al. (2007) found that after 10 years, most patients had stable cognitive testing scores, although attention declined for the group.

In people with MS, direct correlations are difficult to make between plaque location, lesion burden, and cognitive deficits. Lesion location and load varies greatly, and, thus, cognitive profiles are difficult to predict. Sperling et al. (2001) found a relationship between frontoparietal white matter lesion load and cognitive performance on attention-demanding tasks. As in other studies, Sperling et al. (2001) found an association between total lesion burden and cognitive performance, but the strongest associations were seen with regional lesion burden in the frontal and parietal lobes (Figure 14–2). Atrophy, which is independent of lesion burden, may be a useful radiological marker for cognitive involvement (Lanz et al. 2007).

Annual or biannual cognitive screening should be considered; the Multiple Sclerosis Neuropsychological Screening Questionnaire (Medical Advisory Board of the National Multiple Sclerosis Society 2006) is short, sensitive, and specific (Benedict et al. 2003).

Amato et al. (2006) summarized the results from pharmaceutical trials that examined the effects of interferon beta-1b, interferon beta-1a, and glatiramer acetate on cognitive decline. In two small trials of interferon beta-1b, cognitive improvement was demonstrated in the group receiving drug. Patients from the original cohort in the interferon beta-1a trial were followed over 2 years, and the treatment group did better on measures of processing speed and in other cognitive areas. The patients receiving drug and the placebo group in the glatiramer acetate trial showed no cognitive decline after 2 years, but this may be an insufficient amount of time to detect change. Natalizumab may reduce the risk of cognitive worsening, but long-term studies are needed.

It is not known if agents for fatigue, such as amantadine, 4-aminopyridine, and modafinil, improve cognition (Amato et al 2006). Donepezil has been studied in a number of trials of mildly, moderately, and severely cognitively affected patients with MS, and most trials show a positive effect on cognition (Porcel and Montalban 2006).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organ systems, including the CNS. Many studies report that 50% or more of affected

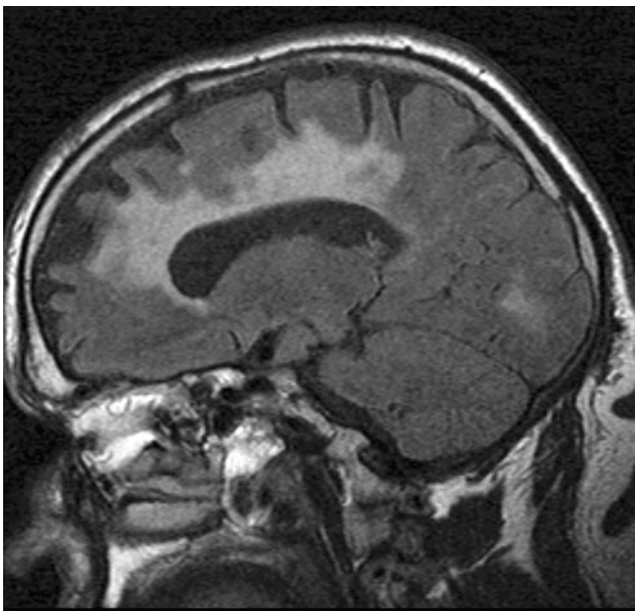

FIGURE 14–2. Magnetic resonance imaging fluid attenuation recovery sagittal image demonstrating significant periventricular white matter hyperintensity oriented perpendicular to the long axis of the lateral ventricle and extending through the deep white matter into subcortical areas.
There is also greater than expected sulcal widening consistent with mild atrophy.

persons will experience neuropsychiatric symptoms at some point during their illness (Berlit 2007; Bruyn 1995; Emori et al. 2005; Harrison and Ravdin 2002).

The neuropsychiatric syndromes defined by the American College of Rheumatology (1999a) include cognitive dysfunction. *Cognitive dysfunction* is defined as a decline from a higher level of functioning in any or all of the cognitive domains (simple or complex attention, reasoning, executive skills, memory, visuospatial processing, language, and psychomotor speed) (American College of Rheumatology 1999b).

Many factors can influence cognitive functions in people with SLE, such as medications, metabolic derangements, underlying psychiatric disorders, and cerebrovascular disease (Ad Hoc Committee on Lupus Response Criteria 2007). The presence of cognitive dysfunction varies; reports range from 12% to 87% (Ad Hoc Committee on Lupus Response Criteria 2007; Berlit 2007; Harrison and Ravdin 2002) and may be the most prevalent SLE-related disease manifestation (McLaurin et al. 2005). The pattern of cognitive impairment is diverse, but it appears to be a subcortical process (Harrison and Ravdin 2002).

A meta-analysis of 25 studies found that most deficits were in the domains of attention, with lesser involvement of visual memory, verbal memory, and psychomotor speed. Testing of language, visuospatial processing, and concept formation was generally intact. Persons with a prior history of neuropsychiatric syndromes in lupus were more likely to experience cognitive dysfunction (Monastero et al. 2001) and more likely to have severe cognitive impairment. The American College of Rheumatology (1999c) recommends a battery of neuropsychological tests to assess cognition in people with SLE that takes about 1 hour and is valid and reliable (Kozora et al. 2004).

McLaurin et al. (2005) reported on 123 patients with SLE who were followed for at least 3 years for cognitive dysfunction. Most participants were women; their mean age was 41 years. Regular use of prednisone and consistently positive antiphospholipid antibodies were predictive of cognitive dysfunction, as was the presence of diabetes mellitus, depression, and lower levels of education. Regular aspirin use was associated with improved cognition, even if prednisone was being concurrently taken; all ages seemed to benefit, but the effect was strongest in the group over age 48 years.

It is unknown if any particular treatment for SLE will prevent cognitive impairment. Prospective, double-blind, randomized clinical trials need to be done. The relationship between steroid use and the development of cognitive dysfunction is not truly known in SLE (McLaurin et al. 2005). No definite relationship has been found between disease duration, disease activity, and concurrent steroid use in a study of 75 SLE patients (Carbotte et al. 1995; Monastero et al. 2001).

Autoantibodies have been investigated as potential mediators of neuropsychiatric syndromes in SLE. A review of the literature from 1995–2005 by Zandman-Goddard et al. (2007) suggested that cognitive dysfunction was associated with seven different antibody types. The antibodies were found in serum and/or CSF, and none was specific for cognitive dysfunction. The antibodies most commonly associated with SLE-associated cognitive dysfunction were anticardiolipin antibodies. Other antibodies associated with cognitive dysfunction were antineuronal, anti-*N*-Methyl-D-aspartate (NMDA) receptor, antiganglioside, lupus anticoagulant, anti-SSA/Ro, and antiserum lymphocytotoxic antibodies. Menon et al. (1999) found that persistently elevated anticardiolipin antibodies over a 2- to 3-year period were associated with cognitive dysfunction, specifically in word fluency, concentration, attention, and reaction time. A 5-year prospective study found that persistently elevated IgG anticardiolipin antibodies were associated with decreased psychomotor speed, problems with conceptual reasoning, and executive dysfunction (Hanley et al. 1999).

An animal model has been developed to test the hypothesis that anti-DNA antibodies enter the CNS through a breach in the blood brain barrier, cross-react with

NMDA receptors, and cause cytotoxicity in hippocampal neurons (Kowal et al. 2004). In this study, memantine prevented neuronal damage in mice. Another study showed a relationship between the presence of anti-NMDA receptor antibodies and visual memory dysfunction (Omdal et al. 2005); however, Harrison et al. (2006) did not find this association. Trials of memantine and modafinil are underway. More research is needed to understand why cognitive dysfunction develops and what preventive strategies can be employed.

Inflammatory/Paraneoplastic

Limbic encephalitis may be viral or nonviral in etiology. Nonviral limbic encephalitis can result from antibodies to proteins of the CNS. Broadly, two categories of antigens have been identified: 1) intracellular or classical paraneoplastic antigens (Hu, Ma2, among others), and 2) cell membrane antigens, including the voltage-gated potassium channels (VGKC), NMDA receptors, and uncharacterized others expressed in hippocampal neuropil and cerebellum (Tüzün and Dalmau 2007). Limbic encephalitis is characterized by short-term memory impairment, complex partial temporal lobe seizures, and psychiatric symptoms. Signal abnormalities in the mesial temporal lobes without contrast enhancement are the typical MRI findings (Vernino et al. 2007) (Figure 14–3). Assays for anti–Ma, Ta1, and Ta2 antibodies, CV2 autoantibody, antineuronal nuclear and anti–Purkinje-cell antibodies, anti-RI antibody, and paraneoplastic opsoclonus–myoclonus antibody may or may not be positive. Morvan syndrome is an autoimmune disorder affecting both the peripheral and CNS. Patients present with behavioral changes, hallucinations, severe insomnia, autonomic hyperactivity, and neuromyotonia (spontaneous muscle activity). Morvan syndrome may be associated with high levels of VGKC antibodies (Josephs et al. 2004). Treatment of limbic encephalitis includes removal of the underlying tumor, if present, and treatments to remove pathogenic antibodies (plasma exchange) or modulate the immune response (steroids or immunosuppressants).

Granulomatous angiitis of the CNS is an extremely rare condition. As with some of the mitochondrial myopathies, patients can present with headaches and grand mal seizures. MRI may resemble glioblastoma. Treatment is with glucocorticoids, often with the addition of cyclophosphamide.

Patients with Hashimoto's encephalopathy, also known as steroid-responsive encephalopathy, associated with autoimmune thyroiditis, may present with atypical psychosis, myoclonus, seizures, dementia, and disturbances of consciousness. In a retrospective review of 20 cases, median age at onset was 56 years. Frequent clinical features are tremor in 16 (80%), transient aphasia in 16 (80%), myoclonus in 13 (65%), gait ataxia in 13 (65%), seizures in 12 (60%), and sleep abnormalities in 11 (55%) (Castillo et al. 2006). The presentation may suggest viral encephalitis, CJD, or a degenerative dementia. Liver enzymes may be elevated, and thyroid hormone levels may remain normal. MRI is often normal or shows nonspecific white matter changes on T_2/FLAIR images (Figure 14–4). EEG may be nonspecific. Anti-thyroid antibodies are present. Treatment with high-dose prednisolone (1 g/day for 5 days) can result in significant or full recovery.

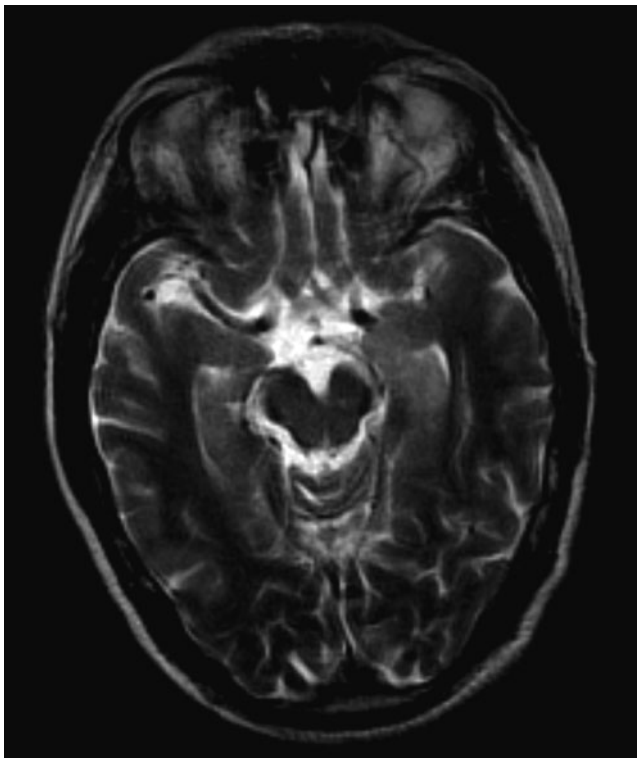

FIGURE 14–3. Magnetic resonance imaging T_2 image demonstrating increased signal in mesial temporal lobes.

Lymphomatosis Cerebri

Lymphomatosis cerebri is a rare variant of primary central nervous system lymphoma that may present as a rapidly progressive dementia with unsteady gait. MRI findings may show an isolated lesion, diffuse leukoencephalopathy without contrast enhancement, or be nonspecific, and CSF may have elevated protein 14–3–3. Diagnosis is often made only after brain biopsy (Rollins et al. 2005; Weaver et al. 2007).

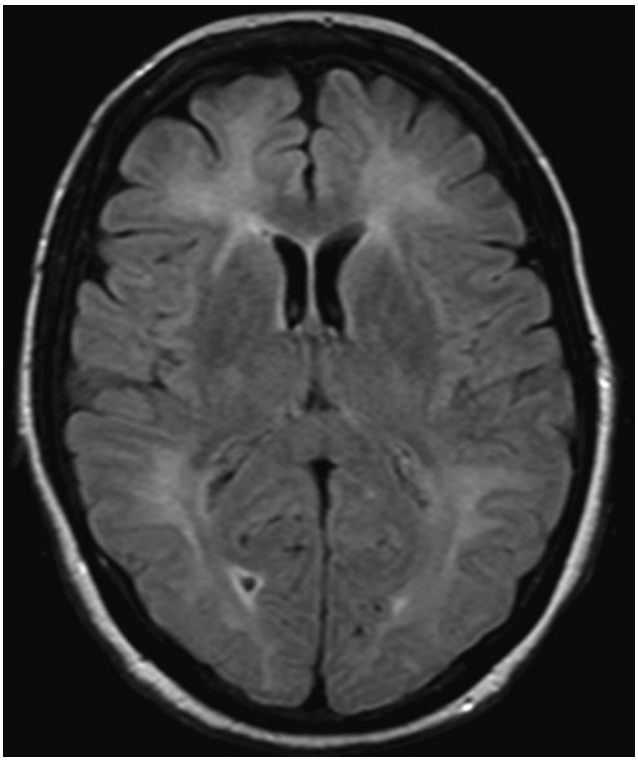

FIGURE 14–4. Magnetic resonance imaging fluid attenuation recovery demonstrating white matter hyperintensities involving the subcortical U fibers.

Diseases Caused by Exposure to Toxic Substances

Ethyl Alcohol

Alcohol can cause acute and chronic complications. Acute alcohol intoxication causes temporary disinhibition followed by sedation and unsteady gait. Heavy alcohol consumption can result in the amnesia of Korsakoff syndrome, alcoholic cognitive impairment, and Marchiafava-Bignami disease. Indirectly, alcoholism may result in hepatic encephalopathy by causing hepatic cirrhosis. Other side effects include the Wernicke triad of ataxia, nystagmus, and ophthalmoplegia. However, this triad is often not present in its entirety. Other complications include myopathy, cardiomyopathy, peripheral polyneuropathy, with predominantly sensory and autonomic deficits and often with a loss of deep-tendon reflexes. Alcohol consumption can also adversely affect vestibular function.

Wernicke-Korsakoff syndrome is a consequence of thiamine deficiency as a result of poor nutrition. It is accompanied by an amnesia that is both anterograde and retrograde. Patients have difficulty forming new memories, and old memories are less distinct. They confabulate. They may mix up information from different time points or make up new stories usually with some element of factual information. When one patient was asked who the lady next to him was, pointing to his wife, he stated, "They say she's my wife."

On neuroimaging, one may see atrophy of the brain in general and, more specifically, the cerebellum, areas of increased T_2/FLAIR signal in midline periventricular structures, and atrophy of the anterior diencephalon and mammillary bodies (Figures 14–5 and 14–6).

Marchiafava-Bignami disease is a dissociation disorder from acute demyelination of the corpus callosum. Patients have attentional deficits, language difficulty, personality changes, and signs of interhemispheric disconnection (apraxia, agraphia, and left-hand anomia) (Berek et al. 1994).

Postirradiation Encephalomyopathy

Ionizing radiation for the treatment of brain tumors can cause damage to double-stranded DNA, RNA, proteins, lipids, and cellular membranes. Radiotherapy-induced cerebral injury generally can be classified by its time of onset as acute encephalopathy, early-delayed, delayed, and late-delayed forms. Delayed forms are typically not reversible. Late-delayed cerebral injury can occur months to years after treatment if the brain was included in the radiation portal (Duffner et al. 1985). Cognitive consequences range from short-term memory impairment to dementia (Imperato et al. 1990). The following is a case evaluated by one of the authors (Figure 14–7).

Case 1

A man in his 70s developed progressive memory loss and language deficits four decades after irradiation for an unspecified intracranial tumor. He had disproportionate atrophy of the left temporal lobe corresponding to the radiation therapy window, which was indicated by permanent tattoos on the left side of his head. Although lobar atrophy secondary to Alzheimer disease or frontotemporal dementia could not be completely excluded, the clinical localization of his symptoms, neuroimaging, and radiation window tattoo made late-delayed radiation a more likely diagnosis.

García-Pérez et al. (1994) correlated specific neuropsychological injury with the total brain irradiation dose but also with the structures located in the cone-down fields of irradiation. Patients deteriorated mainly in visual

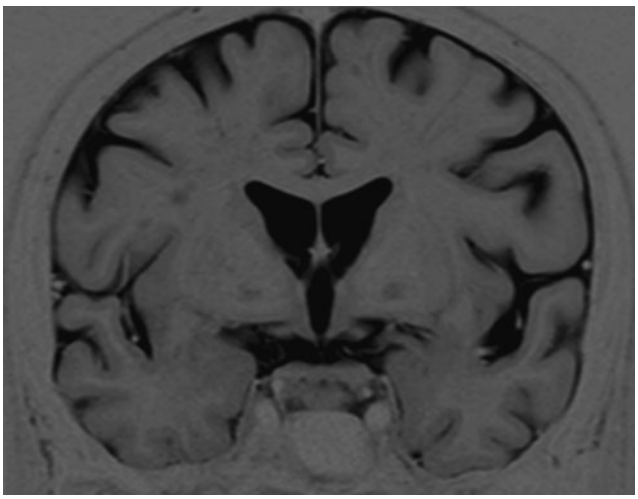

FIGURE 14–5. Magnetic resonance imaging true inversion recovery image demonstrating atrophy of the mammillary bodies.

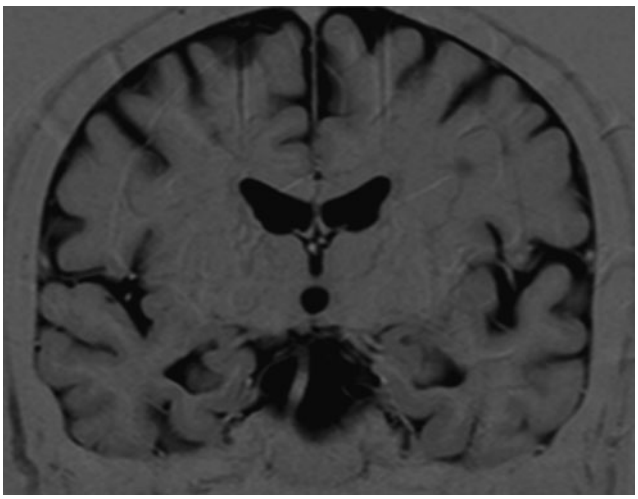

FIGURE 14–6. Magnetic resonance imaging true inversion recovery image demonstrating atrophy of the fornices and hippocampi.

attention and memory but also significantly in verbal fluency and in all subtests of performance IQ tests, when compared with the control groups.

Heavy Metals

Many metals, including lead, mercury, arsenic, manganese, and bismuth, have been associated with cognitive impairment. Lead may produce anemia, abdominal pain, aminoaciduria, bone changes, and peripheral and CNS damage. Lead encephalopathy results in impaired attention, concentration, and memory. Emotional lability and psychosis also may occur. Inorganic mercury poisoning causes stomatitis, irritability, tremor, and peripheral neuropathy. Organic mercury causes parethesias, ataxia, and visual problems. Arsenic can cause myelopathy, peripheral neuropathy, optic neuropathy, somnolence, disorientation, and impaired memory. Manganese toxicity can cause parkinsonism with gait disturbance, tremor, increased muscle tone, memory problems, aggressiveness, and hallucinations. Bismuth toxicity can result in depression, anxiety, hallucinations, and delusions (Supino-Viterbo et al. 1977).

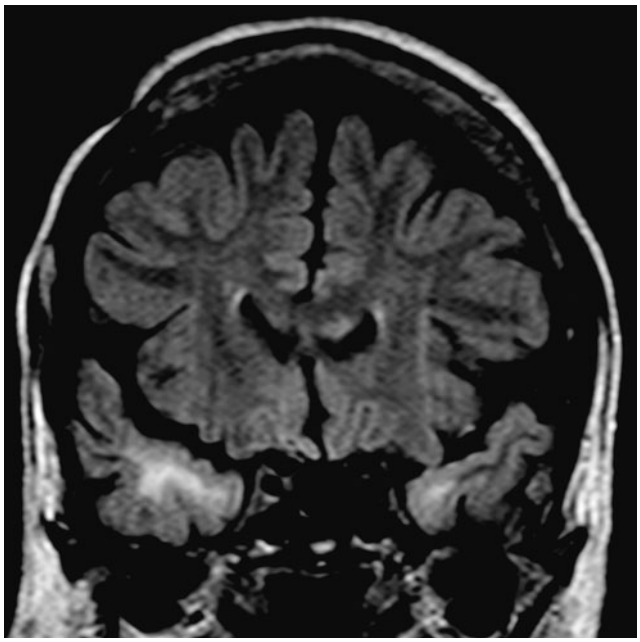

FIGURE 14–7. Magnetic resonance imaging fluid attenuation recovery coronal section demonstrating white matter hyperintensities in bilateral temporal lobes. The right side, which received the greatest amount of radiation, is significantly more affected than the left side.

Cancer Chemotherapy

Cyclosporin may produce leukoencephalopathy. Other chemotherapeutic agents can produce multifocal inflammatory leukoencephalopathies. Symptoms include subacute confusion, seizures, and focal neurological symptoms and may last long after the medications have been stopped. Steroids may help reduce the symptoms.

Diseases Caused by Vitamin Deficiency

Beriberi is caused by thiamine (vitamin B_1) deficiency. This may result from poor diet such as high consumption

of milled rice, severe gastrointestinal disease, alcoholism, HIV infection, gastric bypass surgery, and even hyperemesis gravidarum. Clinical manifestations include apathy, fatigue, irritability, depression, and poor concentration. "Dry beriberi" symptoms include peripheral neuropathy, paresthesias, weakness, pallor, wasting, and hepatomegaly. "Wet beriberi" is associated with cardiac symptoms—edema, tachycardia, and cardiomegaly.

Pellagra is a systemic disease resulting from severe niacin deficiency due to severe malnutrition, alcoholism, and anorexia nervosa. Clinical manifestations include dermatitis resembling sunburn, diarrhea, and dementia. Features of pellagra encephalopathy include confusion, clouding of consciousness, and myoclonus (Serdaru et al. 1988). Symptoms respond to treatment with nicotinic acid.

Cyanocobalamin (B_{12}) is an essential cofactor in the conversion of homocysteine to methionine. Vitamin B_{12} deficiency results in macrocytic anemia and subacute combined degeneration, a disorder of the posterior and lateral columns of the spinal cord resulting in loss of vibratory and position sense, ataxia, weakness, and loss of sphincter control. Optic neuropathy, memory dysfunction, and encephalopathy may ensue. Psychotic symptoms may also occur with or without anemia or spinal cord symptoms. Outright dementia with memory loss is rare. Vitamin B_{12} deficiency may be caused by poor nutrition, loss of intrinsic factor, or gastric bypass surgery. Exposure to nitrous oxide anesthesia may precipitate symptoms in otherwise asymptomatic patients with low vitamin B_{12} values. Copper deficiency may also result in subacute combined degeneration.

Folate modulates the transmethylation and the transsulfuration pathways of homocysteine elimination. Several studies have found an association between low levels of folate and cognitive impairment in the elderly (Hassing et al. 1999), but folic acid deficiency is unlikely today because the U.S. Food and Drug Administration has required folic acid fortification of U.S. grain products (140 μg folic acid per 100 g) since January 1998, with the goal of reducing neural tube defects.

Severe deficiency of vitamin E can result in spinocerebellar degeneration with gait unsteadiness, ataxia, hyporeflexia, loss of both vibratory and joint-position sensations, limitations in upward gaze and strabismus to long-tract defects, profound muscle weakness, and visual field constriction. If prolonged severe deficiency occurs, complete blindness, dementia, and cardiac arrhythmias may develop (Tanyel and Mancano 1997).

KEY POINTS

- Many medical conditions can cause chronic encephalopathies.
- It is important to assess medical status when evaluating patients with cognitive impairment.
- A careful history and exam can uncover important clues to the existence of a potentially reversible dementia.
- Patients with encephalopathy may have more than one cause of cognitive impairment. Each potential cause suggested by history, exam, or tests needs to be considered and assessed.

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CHAPTER 15

Psychiatric Disorders in People With Dementia

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Introduction

Although the presence of psychiatric symptoms is not required for the diagnosis of dementia, almost all dementia patients will experience neuropsychiatric symptoms. Both clinic-based and epidemiological studies suggest that up to 90% of elderly dementia patients will experience at least one symptom of any severity over their illness course (Aalten et al. 2005; Steinberg et al. 2003; Tariot et al. 1995). Such symptoms include delusions, hallucinations, aggression, depression, apathy, and disinhibition. Among dementia participants in the Cache County Study on Memory, Health and Aging, the largest community-based longitudinal cohort study of dementia (Breitner et al. 1999), the most prevalent symptoms were apathy (27%), depression (24%), and agitation (24%) (Lyketsos et al. 2000).

Far from mere annoyances, neuropsychiatric symptoms in dementia have been linked to more rapid cognitive and functional decline (Lopez et al. 1999; Magni et al. 1996; Ropacki and Jeste 2005), greater patient and caregiver distress (Rabins et al. 1982, 2006; Shin et al. 2005; Tan et al. 2005), and earlier institutionalization (Magni et al. 1996; Steele et al. 1990). Severe symptoms can threaten the safety and welfare of the patient and others. A depressed patient, for example, may not maintain adequate food intake; an apathetic patient may become severely deconditioned or develop decubiti; or a physically aggressive patient may harm staff or residents in a nursing home.

Inadequate Knowledge of Effective Therapies

Despite the high occurrence of and morbidity caused by the neuropsychiatric symptoms of dementia, well-studied

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and consistently effective treatments currently are lacking. Support for the many nonpharmacological treatment options is limited as well (Livingston et al. 2005) (see also Chapter 17 of this volume, "Behavioral and Environmental Management").

No pharmacotherapeutic agent has a U.S. Food and Drug Administration (FDA) indication to treat any neuropsychiatric symptom in dementia. The most compelling evidence for efficacy exists for the treatment of depression (Lee and Lyketsos 2003), but even here data are inconsistent, and most studies included only Alzheimer patients even though 25%–40% of elders with dementia suffer from other brain diseases. Although multiple clinical trials suggest benefit of atypical neuroleptics for psychosis and agitated behaviors in dementia, these agents now carry an FDA warning because of increased mortality risk in elders with dementia, and a recent study demonstrated that when treatment benefits were balanced against side effects, atypical neuroleptics in dementia offered little benefit over placebo (Schneider et al. 2006). For some common syndromes in dementia such as apathy and executive dysfunction, only sparse treatment studies exist, mostly at the case series level.

Symptoms Versus Syndrome: What Is Being Treated?

Much of the current inadequacy in treatment guidance stems from a lack of definitions for neuropsychiatric phenomena in dementia. The physician treating dementia patients with neuropsychiatric comorbidity soon realizes that few of the phenomena observed fit neatly into any DSM-IV-TR category. In the case of depression, for example, more severely demented persons often cannot report symptoms such as guilt and suicidal ideation, which would support a DSM-IV-TR diagnosis of major depressive disorder. In addition, there are significant differences in the frequency of many symptoms reported by elderly patients with and without dementia (Zubenko et al. 2003). For example, delusions are more common in depression of Alzheimer disease than in late-life depression (Zubenko et al. 2003).

To make matters more complicated, certain phenomena can be described both as an individual symptom and as a syndrome. Apathy can be an isolated symptom or a syndrome including, but not limited to, decreased motivation and impaired ability to persist in activities (Marin 1991). Furthermore, apathy can also occur as an individual symptom in another syndrome, such as executive dysfunction syndrome.

Faced with a caseload of depressed, psychotic, apathetic, and disinhibited dementia patients seeking help and a limited understanding of both the phenomenology and treatment of these symptoms, what is the physician to do?

Neuropsychiatric Symptoms in Dementia Are Treatable

Clinical experience suggests that many neuropsychiatric symptoms improve with or without treatment. Despite the inconsistent findings of treatment studies for depression and psychosis in dementia, a significant subset of patients do improve with, and are able to tolerate, antidepressants and neuroleptics. Effective treatment strategies are typically comprehensive in scope, employing a variety of nonpharmacological strategies (e.g., caregiver support and education, behavioral interventions) in addition to pharmacotherapy. In order to devise an effective treatment plan, a comprehensive assessment is required to, as best as possible, define the disturbance and to ascertain additional factors that may be causing or exacerbating symptoms (e.g., pain, infection, overstimulating environment).

In this chapter, we use a case-study approach to discuss five common neuropsychiatric phenomena seen in persons with dementia: depression, psychosis, apathy, executive dysfunction syndrome, and agitation/aggression. Following each case presentation, current understanding of phenomenology is reviewed and guidance provided regarding clinical assessment and development of a treatment plan.

Depression

Case 1

Mrs. C, a 72-year-old woman with moderate Alzheimer disease, is brought by her daughter to her physician because of concerns about behavioral changes. "She seems angry a lot and is less interested in things. She cries nearly every day," says her daughter. "She used to enjoy helping me with housework, but now she just sits in the living room with the TV on and sulks. She doesn't seem to enjoy anything, even when the grandchildren visit. Twice in the past month, she has said that I'm not her 'real' daughter, that I'm a stepdaughter, which is not true, and that I want to take her money and place her in a nursing home. I'm worried my mother is depressed."

On examination, Mrs. C scores 15/30 on the Mini-Mental State Examination. She reports her mood is "fine" and denies all depression symptoms. Her affect is mildly constricted and irritable, but she does occasionally smile and laugh appropriately. "I have no complaints," she says. "I like to take life as it comes." When

probed about her concerns regarding her daughter's identity and motives, she smiles tensely and states with a guarded demeanor, "Let's just say she and I have a few disagreements."

Overview

Assessing and diagnosing depression in dementia can be challenging. Fluctuations in mood and behavior are common in dementia patients. Because these patients often "live in the moment," a cross-sectional assessment of their mental status may be insufficient to detect depression; conversely, a mental status exam finding of depressed mood may reflect symptoms that occur fleetingly, if at all, outside of the clinic setting. For this reason, a reliable informant is essential. Even when symptoms are elicited, diagnosing depression in dementia can be difficult. Cognitively impaired patients often do not communicate the sadness, low vital sense, and decreased self-worth that are hallmarks of DSM-IV-TR depressive syndromes. Nevertheless, depression in Alzheimer disease and other dementias is common and may be undertreated.

Epidemiology

Prevalence estimates for depression in dementia vary from 1.5% to 90% (Lee and Lyketsos 2003; Weiner et al. 1994; Zubenko et al. 2003). This wide range reflects the heterogenous methods used to both assess and define depression (Lee and Lyketsos 2003; Olin et al. 2002). Most commonly, frequencies in the clinical setting for major depressive disorder (MDD) are in the 20%–25% range, with minor depression found in an additional 20%–30% (Lyketsos and Lee 2004; Olin et al. 2002; Zubenko et al. 2003). Population studies, which have the advantage of being less subject to referral bias, have demonstrated similar frequencies (Lyketsos and Lee 2004). In the Cache County Study, a community-based cohort of subjects with all dementia types followed for over 5 years (Lyketsos et al. 2000; Steinberg et al. 2003, 2008), the baseline prevalence of depression was 24%, the 18-month incidence was 18%, and cumulative prevalence over 5 years was 77%. In the Cardiovascular Health Study, another longitudinal cohort study, prevalence of depression in dementia was 32% (Lyketsos et al. 2002).

Diagnosis of Depression in Dementia

The diagnosis of dementia among Alzheimer disease patients is not straightforward for many reasons. Persons with Alzheimer disease and other dementias may not remember symptoms. Aphasias may also impede the ability of dementia patients to communicate their inner state. For these reasons, obtaining information from a reliable informant is essential. The challenges of diagnosing depression in dementia, however, go beyond patients' difficulties in memory and communication; clinicians and researchers have long realized that depression in dementia in some ways differs from depression in cognitively intact persons. Thus, reliance on DSM-IV-TR criteria may result in significant underestimation. In precisely what ways depression in dementia is different and how to most accurately classify the phenomenon remains uncertain, and most of the current research focuses on depression specifically in Alzheimer disease.

In comparing DSM-III-R (American Psychiatric Association 1987) symptoms in depressed elderly outpatients with and without Alzheimer disease, Zubenko et al. (2003) found differences in the frequency of many symptoms. Alzheimer disease patients were less likely to report feelings of worthlessness or guilt, thoughts of death or suicide, and sleep disruption. They were more likely to report diminished concentration or delusions and hallucinations. Although approximately 90% of subjects in this sample with or without dementia reported low mood, other experts caution to be wary that elderly patients with depression often do not report or exhibit depressed mood and can present with a "depression without sadness" (Gallo and Rabins 1999).

Some research has focused on identifying symptom constellations or "clusters" that may best define the depression syndrome of Alzheimer disease (Aalten et al. 2003; Frisoni et al. 1999; Mirakhur et al. 2004; Robert et al. 2005). One study of Alzheimer disease subjects in the Cache County cohort (Lyketsos et al. 2001a, 2001b) used latent class analysis to identify a syndrome affecting 27% of the sample that was syndrome characterized by depression, irritability, or anxiety in addition to one or more associated symptoms (e.g., aggression, psychomotor retardation, delusions, sleep or appetite disturbance). Consistent with the conclusions of Gallo and Rabins (1999), depressed mood was not required to diagnose the depressive syndrome, and, consistent with Zubenko et al. (2003), delusions figured prominently. The criteria for Alzheimer-associated affective disorder are displayed in Table 15–1. Although these criteria include both depression and euphoria, studies suggest that the frequency of mania in dementia is low (1%–4%) (Aalten et al. 2005; Lyketsos et al. 2000).

Taking a different approach to classification, a 2000 National Institute of Mental Health workgroup empirically developed provisional criteria for "Depression of Alzheimer Disease" (dAD) (Table 15–2) (Olin et al. 2002). Modeled on DSM-IV criteria for MDD, these criteria dif-

TABLE 15–1. Proposed diagnostic criteria for Alzheimer-associated affective disorder (specify: psychotic or nonpsychotic)

Alzheimer disease by National Institute of Neurological and Communicative Disorders/Stroke and the Alzheimer's Disease and Related Disorders Association criteria
A prominent disturbance of affect, disruptive to the patient or care environment and representing a change from the patient's baseline, as evidenced by the presence of one or more of the following symptoms:
Depression
Irritability
Anxiety
Euphoria
Associated symptoms, also representing a change from baseline, that are less prominent than the disturbance of affect. One or more of the following must be present:
Aggression
Psychomotor agitation
Delusions
Hallucinations
Sleep disturbance
Appetite disturbance
The symptoms within B and C above cluster together in time and occur most days, and the disturbance has a duration of 2 weeks or longer.
The disturbance has its first onset after (or within 2 years before) the onset of cognitive symptoms that eventually progress into dementia.
The disturbance cannot be explained in its entirety by another cause, such as a general medical condition, medication, caregiver approach, environmental precipitant, or life stressor (such as relocation of residence or death of a spouse).

Source. Reprinted from Lyketsos CG, Breitner JC, Rabins PV: "An Evidence-Based Proposal for the Classification of Neuropsychiatric Disturbances in Alzheimer's Disease." *International Journal of Geriatric Psychiatry* 16:1037–1042, 2001. Used with permission.

fer by requiring presence of only three symptoms (vs. five in DSM-IV), allowing for symptoms to be present intermittently instead of nearly every day, adding the criterion of irritability, and specifying the criteria of decreased positive affect or pleasure as "in response to social contact and usual activities." Thus, in Mrs. C's case, her irritability and resistance to the pleasurable activity of going to lunch would be consistent with a dAD diagnosis, and her apparent euthymia at the time of exam would not preclude this diagnosis.

Clinical Assessment

Because Alzheimer disease and other dementias cause impairments in memory, expressive skills, and insight, collateral information is crucial in making a diagnosis of depression. Many patients, such as Mrs. C described previously, are brought to a clinic by a concerned caregiver; others, especially with milder dementias, may present alone, in which case it is advisable for the clinician to request permission to speak to a reliable informant. Given the atypical presentation of depression in dementia and lack of expert consensus diagnostic criteria, use of a rating instrument designed specifically to assess depression in dementia can assist in diagnosis.

The most widely used instrument is the Cornell Scale for Depression in Dementia (Alexopoulos et al. 1988). This 19-item scale is designed to distinguish between symptoms of depression and confounding symptoms that may reflect either the primary dementia process or medical comorbidity (e.g., weight loss from medical illness; poor food intake from loss of sense of taste or smell). The scale requires that information be obtained from both the patient and a reliable informant. When discrepancy exists, as in Mrs. C's case, the clinician makes a judgment in rating each item after taking all reports into account. A score greater than 7 is commonly accepted as indicating clinically significant depression; a score greater than 11, severe depression. The reliability and validity of the Cornell Scale have been established (Alexopoulos et al. 1988), and it has demonstrated sensitivity to treatment outcomes (Lyketsos et al. 2003; Rao et al. 2006).

Some clinicians may prefer to use the Hamilton Rating Scale for Depression (Ham-D; Hamilton 1960). Although not specific to depression in dementia, the Ham-D is widely used and familiar to more clinicians than the Cornell Scale is. The Ham-D may be less reliable than the Cornell Scale, however, in detecting depression, detecting treatment response in clinical trials, and in assessing changes in depression severity (Lee and Lyketsos 2003; Lyketsos et al. 2000).

Although many dementia patients will meet DSM-IV-TR criteria for MDD, some dementia patients will have clinically significant depression symptoms warranting intervention without meeting these criteria. Clinicians should also be wary of the potential for other clinical symptoms or syndromes to be confused with depression in dementia. The most common confounds are apathy, psychosis, and medical comorbidity.

TABLE 15–2. Depression of Alzheimer disease

Three (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. Do not include symptoms that, in your judgment, are clearly due to a medical condition other than Alzheimer disease or are a direct result of non–mood-related dementia symptoms (e.g., loss of weight due to difficulties with food intake).

- Clinically significant depressed mood (e.g., depressed, sad, hopeless, discouraged, tearful)
- Decreased positive affect or pleasure in response to social contacts and usual activities (either 1 or 2 are required)
- Disruption in appetite
- Disruption in sleep
- Psychomotor changes (e.g., agitation or retardation)
- Fatigue or loss of energy
- Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death, suicidal ideation, plan, or attempt
- Social isolation or withdrawal
- Irritability

All criteria are met for dementia of the Alzheimer type (DSM-IV-TR). The symptoms are not better accounted for by other conditions, such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorder.

The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication).

The symptoms cause clinically significant distress or disruption in functioning.

Source. Reprinted from Olin JT, Katz IR, Meyers BS, et al: "Provisional Diagnostic Criteria for Depression of Alzheimer's Disease: Rationale and Background." *American Journal of Geriatric Psychiatry* 10:129–141, 2002. Used with permission.

Apathy is common in Alzheimer disease and other dementias and can co-occur with depression but is also a distinct phenomenon (Levy et al. 1998) that can be mistaken for depression. Apathetic patients lack motivation and initiative but are typically not distressed by their amotivational state. They typically do not display dysphoria, irritability, and delusions. Mrs. C's daughter reported apathy ("She just sits in the living room with the TV on."), but the co-occurrence of tearfulness and irritability suggest more than isolated apathy.

Although the phenomenology of psychotic symptoms in dementia remains to be elucidated, clinical experience and preliminary research suggest that delusions are common in depression of dementia. A study utilizing community-acquired data (Lyketsos et al. 2001a, 2001b) characterized an affective syndrome in dementia in which one-third of depressed subjects experienced delusions, although none experienced hallucinations. A psychotic syndrome was also characterized in which mood symptoms were less prominent and no subject experienced hallucinations. Compared with psychotic depression in nondementia patients, psychotic symptoms in depression of dementia are typically less severe and more transient. Other mood symptoms, such as tearfulness and irritability, are always present in depression and usually of greater severity than the psychosis. Mrs. C's delusion of her daughter being an imposter is a typical delusion of depression: it is intermittent and occurs in the setting of other depression symptoms.

Medical comorbidity can confound a presentation of depression in dementia in two ways: depression can be caused or exacerbated by a variety of medical conditions or medications (e.g., hypothyroidism, use of a beta-blocker), and a medical symptom or medication side effect may be misinterpreted as a symptom of depression (fatigue from anemia, poor appetite from gastrointestinal side effects of a nonsteroidal anti-inflammatory medication) (Steinberg 2008). Thus, comprehensive medical evaluation, including complete blood count, comprehensive chemistry profile, and thyroid function tests, should be obtained on all dementia patients evaluated for depression.

Treatment

Treatment of depression in Alzheimer disease and other dementias is individualized and often empirically based. The continuing uncertainty about the best way to describe and classify depression in dementia precludes the availability of evidence-based therapies. Nevertheless, in most clinicians' experience, the effectiveness of depression treatments in dementia parallels that in the nondemented population. Available therapies are both pharmacological and nonpharmacological.

Nonpharmacological therapies have been found of value. For example, Teri et al. (1997, 2002, 2003) found that behavioral management and a combination of behavioral management and exercise were useful in alleviating

depressive symptoms in persons with Alzheimer disease (see also Chapter 17 of this volume). Traditional psychotherapies, such as interpersonal psychotherapy and cognitive-behavioral therapy, are unlikely to benefit dementia patients because of their cognitive impairments. Patients, however, do benefit from a supportive relationship with a clinician who can comfort, encourage, and imbue optimism. Caregivers benefit from similar support and from treatment for their own depression, if present. This can in turn have positive effects on the patient's own mood. Caregiver education regarding strategies to manage behavioral symptoms (e.g., not arguing or rationalizing, which can exacerbate the patient's distress) and to encourage stimulation and pleasurable activities can also be of benefit.

In most cases that meet criteria for MDD or dAD, an antidepressant should be strongly considered. Data to support efficacy of specific antidepressants or classes of drugs remains limited (see also Chapter 16 of this volume, "Pharmacological Treatment of Neuropsychiatric Symptoms"). In a review of eight placebo-controlled clinical trials of antidepressants for MDD in dementia patients (Lyketsos and Olin 2002), half found the antidepressant to be beneficial. Six studied selective serotonin reuptake inhibitors (SSRIs), one studied imipramine, and one studied the monoamine oxidase inhibitor moclobemide. Limitations of these studies included different criteria for both depression and dementia, different outcome measures used, small sample sizes, and short treatment trials (Lyketsos and Lee 2004). One study (Lyketsos et al. 2003) assessed 41 outpatients with Alzheimer disease assigned to either sertraline or placebo for 12 weeks and found improved depression on sertraline compared with placebo. Successfully treated patients had less functional decline as well, suggesting that depression treatment also may have additional benefits in preserving function. This study is currently being expanded to include a larger subject sample studied over 6 months (Martin et al. 2006) and will use the dAD instead of DSM criteria. A small open-label study of escitalopram (Rao et al. 2006) was the first to demonstrate antidepressant efficacy using the dAD criteria. Published evidence for antidepressants in dementias other than Alzheimer disease is not available.

Because SSRIs are most widely studied in dementia, with several demonstrations of efficacy, they are reasonable first-line antidepressants for most dementia patients (Table 15–3). They are typically begun at the lowest dose (e.g., sertraline 25 mg/day) and increased as needed. In the previous sertraline study, the mean effective dose was 112 mg per day; thus the importance of reaching a therapeutic dose before concluding that an SSRI is not effective cannot be overemphasized. SSRIs are generally well tolerated, with gastrointestinal side effects most common. Other side effects that require monitoring include insomnia and increased confusion. The potential for SSRIs to cause the syndrome of inappropriate antidiuretic hormone (SIADH) is a concern in the elderly, and intermittent monitoring of electrolytes is advisable. Dementia patients are less like to report or be distressed by sexual side effects of SSRIs.

Case 1 *(continued)*

After carefully considering the discrepant clinical reports, Mrs. C's clinician concluded that she was probably suffering from depression. Her daughter reported multiple symptoms occurring over a period of several weeks that met criteria for dAD but not MDD. Although Mrs. C denied most symptoms, she was not deemed a reliable historian because of her dementia. A comment she later made when asked about her memory ("As good as it can be for an old woman") supported the clinician's assessment that she had limited insight. Mrs. C's Cornell Scale score was 10. She began sertraline at 25 mg/day. The dose was titrated to 75 mg/day with minimal benefit, and the patient reported gastrointestinal (GI) upset and loose stools. She was switched to mirtazapine starting at 7.5 mg at bedtime, but this was stopped after 3 days because of severe sedation. Her clinician then began bupropion sustained release at 100 mg/day, and at 150 mg/day, her symptoms significantly improved, and she did not experience GI or other side effects. Her tearfulness remitted, she was more active and easier to engage, including cheerfully assisting her daughter with housework. She still occasionally commented that her daughter is "only a stepdaughter," but with less distress and no longer accused her daughter of stealing.

Psychosis

Case 2

Mr. D's wife calls his physician because she is having difficulty managing his behavior. "He's fine in the morning and early afternoon, but by about 3 o'clock he starts to get moody. He says he needs to 'go home' and see his father, and he doesn't believe me when I remind him his father died 30 years ago. By early evening, he asks where the train station is so he can go home. He's even accused me of stealing his ticket. Once, I showed him a picture of his father's headstone to prove he is deceased and he hit me. I think he needs medicine to calm him down. But I've heard that these medicines can be dangerous and even cause strokes, and you've told me he has a vascular dementia from strokes. Where do I go from here?"

TABLE 15–3. Antidepressants often used for depression in dementia

Class	Examples	Starting dosage (mg/day)	Maximum dosage (mg/day)	Side effect concerns
Serotonin specific reuptake inhibitor	Sertraline	25	150	Gastrointestinal (GI) upset
	Citalopram	10	60	Insomnia
	Escitalopram	5	20	Confusion
	Fluoxetine	10	40	Akathisia
	Paroxetine	10	40	Syndrome of inappropriate antidiuretic hormone
Serotonin-norepinephrine reuptake inhibitor	Venlafaxine	37.5	300	GI upset
	Duloxetine	20 bid	30 bid	Confusion
				Hypertension with venlafaxine
α_1 Antagonist	Mirtazapine	7.5	45	Sedation
Dopamine reuptake inhibitor	Bupropion	100 extended release	450	GI upset
				Hypertension
				Seizure risk

Note. bid = two times a day.

Overview

In this chapter, *psychotic symptom* refers specifically to delusions and hallucinations. Delusions are common in dementia and are among the symptoms most distressing to caregivers. Although they can occur as isolated phenomena, most delusions and hallucinations occur along with other neuropsychiatric phenomena such as depression, agitation and aggression, and irritability. Delusions and hallucinations also can occur from delirium caused by medical problems. As in the case of depression, there is uncertainty as to how to best classify psychotic phenomena in dementia. Management has become more complicated in light of research suggesting that neuroleptics, common treatments for many forms of psychosis, are at best of only modest benefit in dementia and are also associated with safety risks, including increased mortality.

Epidemiology

Many patients with Alzheimer disease and other dementias will experience psychotic symptoms over their illness course. In a meta-analysis of 55 primarily outpatient studies of Alzheimer patients, 41% experienced delusions and 36% experienced hallucinations at some point in illness (Ropacki and Jeste 2005). In the Cache County Study, the prevalence of delusions and hallucinations were 19% and 14%, respectively (Lyketsos et al. 2000); two other large prevalence studies (Aalten et al. 2005; Lyketsos et al. 2002) had similar results. In the Cache County Study, cumulative prevalence over 5 years was 60% for delusions and 38% for hallucinations (Steinberg et al. 2008). No studies have investigated the occurrence of formal thought disorder or abnormality of associations in dementia. Although patients frequently have vague speech with paucity of content, thought disorder similar to that of schizophrenia is considered by most clinicians to be a rare phenomena.

Diagnostic Considerations

As in the case of depression, delusions and hallucinations present themselves differently in persons with dementia than in cognitively intact persons. In addition to the rare occurrence of thought disorder or loose associations, dementia patients rarely report the complex, systematized delusions seen in schizophrenia and psychotic depression or mania. Delusions of persons with dementia tend to be simple and nonbizarre. Common delusions include the belief that their home is not their home (often expressed as a need to "go home" despite being there), that deceased friends and relatives are still living, and that others (often their spouse or children) are imposters. Patients often believe that items they have misplaced or no longer possess have been stolen, often by their spouse or caregiver. These delusions sometimes appear to be outgrowths of their primary cognitive symptoms (e.g., a patient suffering from visual agnosia may not recognize her spouse and conclude he is an imposter).

Similarly, although auditory hallucinations are more common than visual hallucinations in most psychotic disorders, the reverse is true for dementia. Common visual hallucinations are of deceased relatives and friends, as

well as of "young children" or other unspecified "people." Although dementia patients are frequently distressed by their delusions, they often experience these hallucinations nonchalantly; they may even find these "visits" pleasant. An exception is in dementia with Lewy bodies, in which detailed hallucinations are not only common but also often cause distress.

Table 15–4 outlines common differences in delusions and hallucinations in patients with and without dementia. Although visual hallucinations often occur as isolated phenomena, delusions commonly are accompanied by other symptoms, such as depression, irritability, agitation, and occasionally physical aggression. As in the case of depression, some expert-based (Jeste and Finkel 2000) and research-derived (Lyketsos et al. 2001a) criteria for a psychotic syndrome dementia have been proposed. These criteria differ in whether delusions or hallucinations alone are sufficient to make the diagnosis (Jeste and Finkel 2000) or associated neuropsychiatric symptoms are required (Lyketsos et al. 2001b). No dementia-specific psychotic syndrome criteria have been validated or used as an outcome in a treatment trial.

TABLE 15–4. Differences in delusions and hallucinations in psychotic patients with and without dementia

	Patients without dementia	Patients with dementia
Delusions	Systematized Bizarre	Unsystematized Commonplace (children, animals)
Hallucinations	Auditory	Visual

Clinical Assessment

When evaluating a patient with dementia, the clinician must ascertain whether hallucinations or delusions are present, arrive at a differential diagnosis, and devise a treatment plan based on the probable etiology, taking into account symptom severity and distress caused to the patient and/or caregiver. Patients may not spontaneously report these symptoms or may not recall them at the time of the interview. Collateral information from a reliable caregiver is crucial, and it is helpful to inquire specifically about the common presentations of psychosis in dementia (e.g., "Does your father ever believe that items he cannot locate have been stolen?"). In Case 2, Mr. D's symptoms were of sufficient severity that his wife contacted her physician to discuss them. Typical for dementia patients, his symptoms were limited to delusions and were of common varieties (e.g., needing to "go home" when already at home, that his deceased father was living, that his train ticket was "stolen").

Once the presence of delusions or hallucinations is ascertained, the clinician must determine whether these reflect an isolated psychosis or if they are part of another syndrome such as depression or delirium. As discussed previously, delusions are commonly observed in dementia patients suffering from depression, and one study suggests that delusions in dementia caused by depression may occur even more commonly than delusions caused by a primary psychotic syndrome (Lyketsos et al. 2001a, 2001b). Interestingly, hallucinations were reported only in primarily psychotic patients and not in depressed ones. Thus, when assessing delusional dementia patients, symptoms related to mood, sleep, appetite, and behavior are important; if present to a significant degree, the diagnosis of a primary mood syndrome with accompanying delusions should be strongly considered. This distinction may have important implications for pharmacotherapy decisions. If a primary depressive disorder is suspected, the delusions may improve with antidepressant treatment alone, obviating the need for a neuroleptic drug. Unfortunately, consensus in diagnostic guidelines is lacking, and, as discussed previously, research suggests that even primarily psychotic dementia patients may experience comorbid neuropsychiatric symptoms, albeit to a lesser degree. Thus, the decision whether to diagnose a primary psychotic or mood syndrome remains a clinical judgment, taking into account both the presence of comorbid symptoms and their relative severity.

Delusions and hallucinations often occur in the context of a delirium. Features suggesting delirium include clouded sensorium, attentional deficits, marked symptom fluctuation, and disruption of sleep-wake cycle, and these should always be assessed in psychotic dementia patients. Common causes of delirium in the elderly include infections (e.g., urinary tract infection, pneumonia), dehydration, and medication side effects (e.g., anticholinergic side effects, sequelae of polypharmacy).

In Case 2, some "moodiness" and irritability are reported, but these appear to be of milder intensity and also to reflect a reaction to his false beliefs (and, as will be addressed later, to his wife's attempts to correct them). Lack of reported sadness, decreased interest, tearfulness, and sleep or appetite changes argue against a primary depressive disorder. Similarly, lack of sleep disruption or clouded sensorium argues against a delirium. Mr. D's delusions fluctuate, with a steady increase in severity from early af-

ternoon until evening. This diurnal symptom pattern occurs with many neuropsychiatric symptoms in dementia (Cohen-Mansfield 2007) and is not pathognomonic of any specific neuropsychiatric syndrome.

Treatment

Once psychotic symptoms have been identified and assessed as unlikely to be part of another neuropsychiatric syndrome such as depression or delirium, the clinician must decide whether treatment is indicated. Both nonpharmacological and pharmacological options are available. In some cases, no treatment is necessary. For example, the delusions or hallucinations may be mild and intermittent and not distressing to either the patient or caregiver. The clinician may thus need only to educate and reassure the caregiver and/or patient that these symptoms are common in dementia and ensure that the caregiver is responding in an appropriate manner by not arguing or rationalizing with the patient.

More commonly, these symptoms cause some degree of distress for the patient and/or caregiver, and intervention is warranted. In such instances, nonpharmacological strategies should be attempted before considering psychotropic intervention. This is because of the sensitivity dementia patients may have to neuroleptics and recent concerns that have arisen about their efficacy and safety in dementia. Nonpharmacological strategies typically are not aimed at eliminating the delusion and commonly involve brainstorming with the caregiver to implement strategies to lessen the patient's focus on and distress over his or her symptoms.

The first strategy is for caregivers to avoid arguing with or confronting patients about their delusions. At best, such redirection has only brief benefit (the patient forgets) and can often exacerbate their distress and increase suspiciousness that they are being lied to. In Case 2, Mrs. D's insistence that her husband's father was deceased did not lessen his delusion; her attempt to use a photo of his headstone to prove the fact provoked physical aggression. Not rationalizing or correcting is difficult for many caregivers, and they may feel guilty for permitting the patient to believe something false. Education about the goal of responding in ways to lessen distress can be helpful.

Often, caregivers can successfully distract patients distressed by their hallucinations or delusions. Offering a cup of tea together, requesting the patient's assistance with folding laundry or other simple household chores, and changing the topic of conversation are common strategies. A variant of this strategy is to use the content of the patient's delusion to transition onto a less distressing topic. For example, when Mr. D expresses concern about not being able to find the train station, his wife may respond by discussing recent construction occurring in town and transition into a conversation about how difficult finding familiar locations has become.

Another technique for caregivers is to discern the emotion underlying the psychotic symptom and respond to that. For example, when a patient such as Mr. D insists he needs to see his father, Mrs. D, sensing his grief and longing for his father, may respond, "Tell me about your father. What's your favorite thing that you did together?" If successful, this strategy can result in the conversation changing toward pleasurable reminiscence. When patients are frightened by visual hallucinations, they sometimes respond to the reassurance that, "I know these things you see are frightening to you, but I am here and you are safe."

Frequently, these strategies are insufficient to control behavior, and pharmacotherapy is indicated. The mainstays of treatment, as in nondementia psychotic conditions, are neuroleptics. Many clinicians and caregivers understandably worry about instituting neuroleptic treatment. Many of the side effects of both typical and atypical neuroleptics, outlined in Table 15–5, are of special concern in the fragile elderly. Furthermore, an FDA safety alert in 2003 warned of increased risk of cerebrovascular events for the elderly with dementia treated with atypical neuroleptics. In addition, in 2005, the FDA issued a public health advisory that elderly patients with dementia treated with atypical neuroleptics are at 1.6–1.7 times increased risk for mortality, most commonly from infectious and cardiovascular causes, and all atypical neuroleptics carry a black box warning to this effect. An independent meta-analysis (Schneider et al. 2005) confirmed this finding and also suggested that typical neuroleptics such as haloperidol are associated with equal or greater mortality risk in this population, and in 2008 a similar black box warning was added for convenional antipsychotics. Whereas six double-blind, placebo-controlled clinical trials of risperidone or olanzapine for psychosis found "modest statistical efficacy" (Sink et al. 2005), a more recent large placebo-controlled trial of risperidone, olanzapine, and quetiapine found that although subjects were less likely to stop risperidone or olanzapine because of lack of efficacy, that benefit disappeared when those stopping the study medication because of adverse events were taken into account (Schneider et al. 2006). In other words, subjects were at least as likely to suffer an adverse event necessitating stopping neuroleptic as they were to benefit from the medication.

In light of these findings, most experts still agree that neuroleptics have an important role in the treatment of psychosis in dementia, but only in some circumstances. Many patients do not respond to adequately nonpharma-

TABLE 15–5. Neuroleptic side effects

Neuroleptic side effect	More common with atypical than typical neuroleptics	Of special concern in elderly with dementia
Sedation	✓	✓
Unsteadiness/falls		✓
Parkinsonism		✓
Anticholinergic side effects		
Dry mouth		✓
Constipation		✓
Urinary retention		
Blurry vision		
Tachycardia		
Akathisia		
Tardive dyskinesia		
Neuroleptic malignant syndrome		
Diabetes risk/ exacerbation	✓	✓
Metabolic syndrome	✓	

cological interventions alone, even when administered in a sophisticated manner by caregivers. Despite concerns about adverse effects, research and clinical experience do support that at least a subset of dementia patients both benefit from and tolerate neuroleptic treatment. Rabins and Lyketsos (2005) have outlined the three circumstances in which neuroleptic treatment of psychosis in dementia is indicated: 1) identifiable risk of harm to patient or others is present, 2) distress caused by symptoms is significant, and 3) nonpharmacological treatment interventions have been unsuccessful and symptom relief is important. An open discussion of indications, benefits, risks, and alternatives should occur with the caregiver and/or patient before initiating treatment. Starting doses should be low (e.g., haloperidol 0.25 mg/day, orally; quetiapine 12.5 mg/day, orally), with slow increase as needed. Table 15–6 indicates common starting and maximum doses of neuroleptics for which published studies in dementia exist. The need for continued treatment must be reassessed frequently, with regular attempts to taper or stop the medication, or alternatively, a clear rationale for continued use.

TABLE 15–6. Typical initial and maximum doses of neuroleptics for treatment of psychotic symptoms in dementia

Neuroleptic	Typical initial dose range (mg)	Typical maximum dose range (mg)
Haloperidol	0.25–0.5	1–2
Risperidone	0.25–0.5	1–2
Olanzapine	2.5	10–12.5
Quetiapine	12.5–25	150–200

Case 2 *(continued)*

Mr. D's physician scheduled an extended appointment with Mrs. D to educate her about the nature of delusions in dementia and the importance of not arguing or rationalizing with him when he is delusional. He referred her to a dementia-trained geriatric social worker to assist in developing strategies to respond to her husband's behavior. During this counseling, Mrs. D mentioned she and her husband used to ballroom dance, and she discovered that putting on music and dancing together in the late afternoon often prevented or minimized the emergence of delusions about needing to "go home" or find the train station. She found reminiscing about his father with a scrapbook a much more effective strategy than trying to convince him that his father was deceased. Sometimes, while looking at the scrapbook, he would cry and ask where his father was; she would hold his hand silently until his crying ceased and then announce that it was time for coffee.

Six months later, his delusions became more severe and were only mildly relieved by the previous strategies. Several times, he raised his fists at Mrs. D in a threatening manner. After a discussion about the risks and benefits of neuroleptic treatment, she and her physician agreed that a trial was warranted. Mr. D was treated with risperidone 0.25 mg/day, orally, and at a dose of 0.75 mg/day orally, his symptoms improved and he experienced no side effects. After another 6 months, risperidone was successfully tapered and discontinued, and the previous nonpharmacological interventions again sufficed.

Apathy

Case 3

"She just sits in a chair and does nothing all day," says Mr. E during a routine neurology follow-up for his wife, who has moderate Alzheimer disease. "I take her out for lunch and shopping, but within a half hour she says she's

had enough and is ready to go home. I even tried to enroll her in adult day care, but she refused to get on the van. Her friends say that as long as she seems content, I should respect her decision to just sit around. But my daughter says it hurts to see her mother like this and that it's as if the joy of life has gone out of her eyes."

Overview

Mr. E is not alone in his concerns because apathy is the most common neuropsychiatric symptom of dementia. Apathy may be the earliest occurring feature in dementias in the elderly, preceding even early cognitive impairment (Onyike et al. 2007). As in depression and psychosis, uncertainty remains as how to best characterize apathy in dementia; it can be conceptualized as both a discrete symptom or as a syndrome. Apathy can occur alone and as a symptom of another syndrome (e.g., depression). The lack of interest and motivation from apathy may be interpreted by some, such as Mr. E and his daughter, as a problem warranting medical assessment; others, such as Mrs. E's friends, may see it as a choice to be respected or as an inevitable and untreatable consequence of the dementia process. Severe apathy can be associated with physical deconditioning (Politis et al. 2004), and research suggests an association between apathy and increased impairment in performing basic activities of daily living (Frees and Cohen 1992). It can be challenging for clinicians to decipher the extent to which reassurance is more appropriate than pharmacotherapy or behavioral interventions. Despite the burden caused by this symptom, consistently effective evidence-based interventions are lacking.

Epidemiology

Apathy prevalences in community samples are as high as 80% (Onyike et al. 2007). In the Cache County Study, apathy was the most common neuropsychiatric symptom in dementia, with a prevalence of 27% (Lyketsos et al. 2000). The cumulative prevalence was 71% at 5-year follow-up (Steinberg et al. 2008). Similar high rates of apathy were found in another large longitudinal community-based study (Aalten et al. 2005). A recent review of nursing home–based studies found apathy prevalence to vary widely, from 17% to 84% (Zuidema et al. 2007). This variation was attributed to differences in definitions of dementia as well as of methods of assessment.

Diagnostic Considerations

Current expert consensus supports the existence of a distinct apathy syndrome (Lueken et al. 2007; Marin 1991; Starkstein et al. 2001). Despite support for the apathy syndrome's existence, a universally accepted definition remains elusive. As formulated by Marin (1990), the apathy syndrome includes a decrease in motivation and initiative, emotional blunting and indifference, and impaired ability to persist in activities. The most commonly used measure of apathy in the elderly is the Apathy Evaluation Scale (AES) (Marin et al. 1991). Although the AES is widely used in clinical research, it is rarely used by clinicians either to detect the presence of apathy in patients or to monitor treatment response. An abbreviated 10-item version of the AES (AES-10) has been developed and adapted specifically for dementia patients (Lueken et al. 2007). For the present, clinicians caring for patients such as Mrs. E face the challenge of using their clinical skills and judgment to diagnose and treat a syndrome that remains imperfectly defined and categorized.

Clinical Assessment

Inquiry about depressive symptoms is crucial in diagnosis of an apathy syndrome. In addition, whereas depressed patients often appear distressed by their symptoms, apathetic patients often appear content. Mr. E's report that his wife appeared content would thus be more supportive of apathy than depression. As commonly occurs with apathy in dementia, he and his children are more distressed by these behaviors than is the patient.

Executive dysfunction syndromes often also include apathy, and these are reviewed in the following section. Many medical conditions cause or contribute to apathy in dementia. Medically frail patients often have low vitality and diminished motivation. It is important to ensure that decreased activity caused by pain or discomfort is not mistaken for apathy. The standard evaluation of a patient with recent onset of apathy should include a laboratory study; anemia, metabolic abnormalities, and hypothyroidism are among the medical conditions that can cause apathy.

Treatment

Often the most beneficial intervention, especially in milder cases, is education of the caregiver about the nature of apathy as a common feature of dementia. Understanding apathy as an anticipated part of the disease process can lessen the caregiver's frustration and bewilderment. In more severe cases, with accompanying risk such as physical deconditioning, treatment trials are warranted. Because of the limited knowledge available about effective pharmacotherapies for apathy, nonpharmacological interventions should be attempted first in all but the most severe cases.

Caregivers can benefit from brainstorming with a professional to devise behavioral strategies to encourage increased activity. For example, arguing with or exhorting a dementia patient about the importance of engaging in an activity is rarely helpful and can exacerbate both the patient's and caregiver's distress. Techniques caregivers may find helpful include offering gentle commands instead of requests (e.g., "You need to come this way. The van (to day care) is waiting," instead of "Won't you please get in the van now?") and offering single instead of multiple options ("I need your help drying the dishes," instead of "Would you prefer to wash or dry the dishes tonight?") (Steinberg 2008). Having an activity set up in advance (e.g., a card table arranged for gin rummy, coat and gloves laid out for daily walk) can be helpful. Sometimes caregivers will still encounter much resistance despite use of these techniques. A balance needs to be obtained between keeping the patient engaged and avoiding persistent, futile prodding. Caregivers are advised to choose their battles wisely (e.g., getting the patient on the day care van but forgoing getting the patient to help with the dishes), and a nurse or social work counselor with dementia expertise can prove valuable in this regard. Successfully engaging patients in any stimulating activity in turn may have the additional positive effect of decreasing apathy. Politis et al. (2004) found that apathy in dementia patients in long-term care improved with mental stimulation, and the benefit was seen whether patients were assigned to a "mental stimulation kit" intervention or a control "social visit."

Pharmacotherapeutic interventions are difficult to recommend with confidence at present given the paucity of available data, but empirical treatment trials may be indicated when behavioral interventions are unsuccessful or the apathy is so severe that the patient refuses to get out of bed.

The most consistent evidence for benefit, and the only evidence based on placebo-controlled studies, is for cholinesterase inhibitors (Cummings et al. 2005; Mizrahi and Starkstein 2007; Wynn and Cummings 2004). Unfortunately, the degree of benefit is typically small and the positive studies were not designed to measure apathy as a primary outcome (Mizrahi and Starkstein 2007). Nevertheless, cholinesterase inhibitors are standard care for many dementia patients, and some apathetic patients may have the extra benefit of improvement in this behavior. Several other agents have been investigated for treatment of apathy at the case study level, although not specifically in dementia patients. Most enhance dopamine transmission, putatively associated with apathy, and include amantadine (Marin at el. 1995; van Reekum et al. 1995), bupropion (Corcoran et al. 2004; Marin et al. 1995), and methylphenidate (Marin et al. 1995; Padala 2005, 2007; van Reekum et al. 1995). Potential pharmacological treatments and their dosage ranges are displayed in Table 15–7.

Case 3 *(continued)*

Mrs. E's neurologist scheduled a family meeting with Mr. E and his daughter. At this meeting, it came to light that Mr. E himself was not as distressed by his wife's apathy as he initially appeared to be; rather, he was feeling guilty in the setting of his daughter's frequent implications that he was at fault for "allowing mom to wither away." Her neurologist discussed the nature of apathy in dementia and how apathy is an expected part of the disease course for many patients. Both were receptive. Mr. E discovered that his wife was more amenable to activities when he used gentle commands and avoided giving choices, and he was thus able to achieve her going to day care at least three-quarters of the time. A trial of donepezil was begun as part of standard dementia care. Over the next 6 months, some slowing of cognitive decline was noted, but no improvement in apathy, which remained a persistent but manageable symptom over the next several years.

Executive Dysfunction Syndrome

Case 4

"He embarrasses me," complains Mrs. F to the psychiatrist following her 57-year-old husband with early-stage frontotemporal dementia. "Whenever we go to the store, he makes rude comments to other customers, especially women, about their physical appearance. The night he made a vulgar gesture toward a waitress, I wanted to crawl under the table. The waitress laughed and told me privately that as a 70-year-old woman, she was flattered, but how can I take him anyplace now? At home, he paces a lot, laughs for no reason, and says ridiculous things. Some day, I know he'll need long-term care, but what assisted living facility would even take him like this?"

Overview

Mrs. F's description of her husband's sexually inappropriate behavior, disinhibited comments, and frequent pacing suggest an executive dysfunction syndrome (Lyketsos et al. 2004). Such syndromes, related to disruption of frontal-subcortical circuits, are less common in dementia than depression, psychosis, and apathy, although apathy can be a feature of executive dysfunction syndrome. When behaviors such as those exhibited by Mr. F do occur, they can distress and embarrass caregivers and can present a safety

TABLE 15–7. Typical starting and maximum doses of putative treatments for apathy in dementia

Agent	Starting dosage (mg/day)	Maximum dosage (mg/day)
Cholinesterase inhibitors		
Donepezil	5	10
Galantamine	8	16–24
Rivastigmine	3	12
Amantadine	50	300
Bupropion	37.5–75	300
Methylphenidate	2.5–5	20

hazard, whether injury from restless pacing or a slap in the face from an offended party. With limited evidence for effective therapies, treating this syndrome has been described as "very challenging and mostly unsuccessful" (Drayton et al. 2004).

Epidemiology

Given the myriad forms in which executive dysfunction syndrome can present itself, its true prevalence in dementia is not known. The Cache County Study found a point prevalence for disinhibition of 9% (Lyketsos et al. 2000) and a 5-year cumulative prevalence of 31% (Steinberg et al. 2008). For "aberrant motor behavior" (consisting of pacing and repetitive behaviors), an 8% point prevalence and 57% 5-year prevalence were found. Approximately 7%–25% of dementia patients, predominantly men, display sexually inappropriate behavior (Black at al. 2005).

Diagnostic Considerations

Executive dysfunction syndrome can appear in a variety of ways and usually involves some combination of disinhibition and stimulus boundedness. Examples of symptoms in this cluster include sexually inappropriate behavior, pacing, silly comments, eating nonfood objects, and perseverative repetition of phrases. Apathy may also be present. Although executive dysfunction syndrome can occur in all dementias, it is especially common in dementias with prominent frontal-subcortical involvement, such as the frontotemporal dementias and Huntington disease. Because these dementias often affect younger persons such as Mr. F, the behaviors are sometimes interpreted as volitional and reflecting character traits or moral flaws.

Clinical Assessment

Apathy is the most common symptom (Diehl-Schmidt et al. 2006), followed by inappropriate, disinhibited behaviors that frequently co-occur with diminished motivation and initiative. Caregivers, particularly family members, may feel embarrassed and ashamed when discussing patients' disinhibited and inappropriate behavior, particularly when it is sexual in nature. The physician should emphasize to uncomfortable family members that these symptoms are not uncommon in dementia and nearly always related to the brain disease. The physician should inquire about a wide range of disinhibited and perseverative behaviors, including disinhibited comments and gestures, perseverative behaviors (pacing, repetition of a phrase), physical intrusiveness, stimulus boundedness (reaching and grabbing at items), and sexually inappropriate behavior. The disinhibited and hypersexual behaviors characteristic of executive dysfunction syndrome can resemble mania or hypomania.

Treatment

The approach to treating executive dysfunction syndrome in many ways is similar to that of apathy syndrome. In both situations, the physician is faced with behaviors that cause significant distress and for which no consistently effective pharmacological or nonpharmacological treatment is available. The physician must assess symptom severity and disruptiveness to determine whether intervention is needed beyond education of the caregiver about the syndrome, including ensuring the caregiver is aware that these symptoms, although often embarrassing, are not under voluntary control. In Mr. F's case, the symptoms are frequent, disruptive, and cause distress, indicating the appropriateness of further intervention. Given the paucity of evidence for effective pharmacotherapy, nonpharmacological interventions are typically the first approach. For example, if the patient makes inappropriate comments in public, planning a stroll and picnic in a quiet park may be more suitable than dinner in a restaurant followed by a trip to the mall. If the patient touches himself inappropriately, one-piece outfits may decrease this behavior. Patients who pace and wander may benefit from having a secure area where they can pace with minimal risk. Frequent and severe pacing is also an indication to consider a secured living setting, in which units are often specifically laid out to address this behavior.

Despite lack of evidence for effective pharmacotherapy, severe symptoms may warrant empirical medication trials. Case reports and some clinic experience suggest benefit in executive dysfunction syndrome from a variety

of pharmacological agents (Table 15–8), including SSRIs (Opler et al. 1994), mood stabilizers such as valproic acid (McQuistion et al. 1987), stimulants (Rosenblatt et al. 2003), neuroleptics, and amantadine (Drayton et al. 2004). A chart review study of 30 dementia inpatients with executive dysfunction syndrome (Drayton et al. 2004) found 57% of subjects discharged taking amantadine were "much improved," although this study did not take into account concurrent pharmacotherapies. Antiandrogen therapies (e.g., flutamide) may be helpful in dealing with severe hypersexual behavior.

Case 4 *(continued)*

After discussion with her psychiatrist, Mrs. F decided to stop taking her husband to public places such as restaurants, where his behavior was likely to be problematic. She made sure to enlist the help of male friends to watch him so she could continue to socialize on her own. Over the next year, Mr. F's behaviors became more severe. His pacing became nearly constant, and the disinhibited sexual comments became coarser and more frequent. Following a counseling session with his tearful wife, the psychiatrist started amantadine, starting at 50 mg/day, orally. At 100 mg two times a day, his pacing and sexual behaviors improved, but the drug was stopped because of severe hallucinations. Mrs. F subsequently decided to place her husband in a secured assisted-living setting. Over the ensuing months, his sexual behaviors increased further, and he began to inappropriately touch other residents. The evening he was found undressed and aggressively fondling a female resident in her room, he was discharged to an emergency room and from there to an inpatient neuropsychiatry specialty unit. His testosterone level was normal. A trial of flutamide was begun, and his sexual behaviors improved to the point he was able again to be managed in assisted living.

TABLE 15–8. Possibly effective agents for executive dysfunction syndrome

Agent	Starting dosage (mg/day)	Maximum dosage (mg/day)
Selective serotonin reuptake inhibitors		
Sertraline	25	150
Citalopram	10	60
Escitalopram	5	20
Fluoxetine	10	40
Paroxetine	10	40
Mood stabilizers		
Valproic acid	125 bid	1,000–1,500
Carbamazepine	50–100	300
Amantadine	50–100	300
Bupropion	100 slow release	300
Methylphenidate	2.5–5	20

Note. bid = two times a day.

Agitation and Aggression

Case 5

Almost immediately after arrival on the nursing home unit, Dr. G is approached by a nurse: "A woman named Mrs. H was admitted last night. She has dementia and is agitated. She is striking at staff, and last night she punched another resident in the back. She needs something to calm her down."

Overview

Agitation and aggression are common behaviors faced by dementia-care providers in the long-term setting, and are often the precipitants for admission. These patients typically appear distressed, and their presence in the milieu can present a safety risk to staff and residents. Providing care for such patients can demoralize direct-care providers, especially when they are repeatedly struck during care. These behaviors are nonspecific, with a wide range of potential causes, including the previously described neuropsychiatric syndromes, as well as medical and environmental factors. A thorough investigation into the potential etiologies for these behaviors in a specific patient will guide the physician in developing a plan of intervention (Cohen-Mansfield et al. 2007). Meanwhile, the safety risks posed by physical aggression may warrant immediate intervention, such as psychotropic use or inpatient hospitalization, while this evaluation is underway.

Epidemiology

In the Cache County Study, the 1-month prevalence of agitation or aggression was 24% (Lyketsos et al. 2000). The 5-year cumulative prevalence was 44% and lower than the prevalence for depression, delusions, or apathy (Steinberg et al. 2008). Agitation and aggression appear to be more common in long-term care settings, with frequency estimates of 50%–60% (Ballard 2007; Margallo-Lana et al. 2001).

Diagnostic Considerations

Unlike the neuropsychiatric disturbances discussed earlier, there is no clearly defined "agitation syndrome." These

symptoms typically are nonspecific (Cohen-Mansfield et al. 2007) with a wide differential. Potential causes include the primary dementing process (other psychiatric syndromes such as depression and psychosis), a medical problem (e.g., delirium, pain), or provoking factors in either the environment or caregiver approach. These causes, with examples and suggested interventions, are displayed in Table 15–9.

Clinical Assessment

A systematic process of evaluating agitated dementia patients has been formulated by Rabins et al. (2006) and is referred to as the four Ds (describe, decode, devise, and determine). The physician must first be able to *describe* the behavior accurately. The differential diagnosis and workup for a patient who is tearful, irritable, yelling out, pacing, and suspicious much of the day, for example, likely will be different from that of a patient who is usually calm and pleasant but strikes at caregivers when dressed or toileted. Having formulated a precise description of the behavior, the physician attempts to *decode* the cause among the various contributors listed in Table 15–9. Multiple contributing factors are often present. The physician relies on his or her formulation of the likely etiology (or etiologies) to *devise* a treatment plan. Follow-up is crucial to *determine* the effectiveness of the intervention, with adjustments in care plan as needed.

Treatment

Treatment is guided by the presumed cause(s) of the behavior. If a psychiatric syndrome such as depression or psychosis is suspected, treating these syndromes often results in full remission of the behavior. Similarly, treating the putative medical condition (e.g., antibiotics for urinary tract infection; analgesic for pain) can be expected to result in similar improvement. In cases in which environmental or caregiver approach factors may contribute to the behavior, consultation by a clinician with expertise in dementia care can be helpful. Such clinicians, who include physicians, nurses, and social workers, can counsel caregivers on ways to modify these provoking factors (see Table 15–9).

If agitation or aggression poses a safety threat to the patient or others, the physician may need to prescribe temporarily a psychotropic to manage the behavior while the comprehensive evaluation is underway. Negligible evidence-based guidance exists, but low doses of neuroleptics or benzodiazepines (e.g., risperidone 0.25 mg/day, orally, or lorazepam 0.25 mg/day, orally) are commonly used. These may be administered as needed or as a standing dose, depending on symptom severity. For cases in which either no clear etiology is identified or the symptoms persist despite addressing the presumed cause, empirical trials of pharmacotherapy may be indicated. Neuroleptics are most commonly used, especially for physical aggression. Most of the previously discussed neuroleptic clinical trials included subjects with nonspecific agitation as well as those with psychosis. SSRIs such as citalopram may have benefits similar to neuroleptics in treating these behaviors (Pollock et al. 2002, 2007). Anticonvulsants may reduce agitation and aggression in some patients (Meinhold et al. 2005; Porsteinsson et al. 2003; Tariot et al. 1998), although several clinical trials have not demonstrated this benefit (Lonergan et al. 2004; Tariot et al. 2005). Although studies suggest that cholinesterase inhibitors decrease agitation (Cummings et al. 2005; Holmes et al. 2004), this effect is typically mild, and these agents therefore should not be considered first-line treatments for severe agitation or aggression. Benzodiazepines should be avoided because of their association with tolerance, sedation, and increased risk of falls and confusion.

Case 5 *(continued)*

During Dr. G's examination, Mrs. H was irritable with intermittent tearfulness. She said, "I don't know who you are but get away from me!" Her Mini-Mental State Examination score was 13/30. Physical examination was very limited because she attempted to strike Dr. G. Dr. G obtained additional history from Mrs. H's son, who reported that these behaviors had been increasing over the past week and were similar to those occurring during a bout of pneumonia she had experienced the year prior. Dr. G ordered a chemistry panel, complete blood count, chest X ray, and urinalysis and culture. The chest X ray was normal, but her white blood cell count was mildly elevated, and the urine culture revealed a urinary tract infection. Dr. G began antibiotic treatment and also ordered lorazepam 0.25 mg orally or intramuscularly every 8 hours as needed for severe agitation, with a stop date in 2 weeks for reevaluation. Five days after Mrs. H's admission, her son informed staff that he had forgotten to mention that his mother took acetaminophen twice daily for arthritis, and this treatment was reinstituted. When reevaluated by Dr. G 2 weeks after admission, Mrs. H's aggression had resolved, and she was calm and pleasant. Lorazepam had not been used in the preceding 5 days, and the order was not renewed. Dr. G attributed Mrs. H's improvement to several factors: treatment of a urinary tract infection, which had caused mild delirium; reinstitution of her analgesic; and adjustment to her new living environment.

TABLE 15–9. Potential causes of agitation and aggression in dementia

Etiology	Examples	Intervention
Primary disease process	Patient swings fists at staff when he cannot express his needs.	Provide picture board so the patient can point to the picture representing his need.
	Patient with agnosia is distraught when she sees her reflection in the mirror.	Remove or cover mirrors and other reflective surfaces.
Psychiatric syndrome	Patient meets criteria for depression of Alzheimer disease.	Treat with antidepressant.
	Patient is delusional that staff is trying to poison her.	Treat with neuroleptic.
Medical problem	Patient has a urinary tract infection.	Treat with antibiotics.
	Patient with arthritis of his knees grimaces when walking.	Treat with analgesic.
Environmental factors	Patient becomes disruptive during shift changes, when there is commotion.	Engage patient in an activity far from nursing station during change of shift.
	Patient living at home is restless on days when home health aide is not present.	Increase the frequency of home health aide visits.
Caregiver approach	Patient is physically aggressive with his daughter during morning care. She often rushes him because of time pressure.	Hands-on caregiver assessment and teaching by expert dementia care nurse.
	Caregiver frequently argues with or corrects patient.	Counseling session with physician to modify caregiver's approach.

KEY POINTS

- Although consistently effective treatments for neuropsychiatric symptoms are currently lacking, clinical experience suggests most symptoms are treatable.
- Treatment strategies need to be comprehensive, employing nonpharmacological strategies in addition to pharmacotherapy.
- Many neuropsychiatric phenomena, including depression, psychosis, and apathy, may best be classified as syndromes.
- Effective pharmacotherapy for depression and psychosis has been demonstrated in double-blind clinical trials.
- Because of safety concerns, physicians need to carefully weigh risks and benefits of atypical neuroleptics when deciding how to treat dementia patients.
- Although minimal evidence exists for effective treatments for apathy or executive dysfunction syndrome, a variety of nonpharmacological and pharmacological interventions may be beneficial.
- Agitation and aggression are nonspecific symptoms, and treatment strategies should be guided by the presumed cause of the behavior.

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PART IV

Treatment of Dementia

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CHAPTER 16

Pharmacological Treatment of Neuropsychiatric Symptoms

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Literature reviews suggest that up to 90% of patients with dementia will develop significant behavioral problems at some point in the course of their illness (Tariot et al. 1993), a result borne out by population-based studies of behavioral features associated with dementia that conclude that the figure is actually closer to 100% (Lyketsos et al. 2000). The implication is that "behavioral and psychological signs and symptoms of dementia" (Finkel et al. 1996) are major features of dementia and require a thoughtful appreciation of their phenomenology, assessment, and management. In this chapter, we provide an opportunity to offer a personal overview of these topics.

Examples of the behavioral manifestations of dementia include features suggestive of depression, mania, anxiety, psychosis, apathy, and agitation. There have been efforts to propose syndromal criteria for "psychosis" (Jeste and Finkel 2000) and "depression of Alzheimer's" (Olin et al. 2001), but these proposed criteria have not been validated. Cohen-Mansfield (1986) defined *agitation* as "inappropriate verbal, vocal, or motor activity unexplained by apparent needs or confusion." This pragmatic definition emphasizes the clinician's responsibility to first presume that the behaviors have some meaning, even if not immediately perceptible. Shouting or striking out during care should not be dismissed as "agitation" mandating psychotropic therapy when in fact a specific behavioral intervention might be identified. The behavioral changes seen in dementia tend to occur in clusters of signs and symptoms that may vary among patients and within patients over time, rather than as syndromes that we usually recognize

from other psychiatric disorders, presumably reflecting the complex interaction between cognitive deficits and environmental variables. These clusters of signs and symptoms can be both predicted and recognized and can be used as guideposts in the selection of appropriate therapy. That said, it is important to emphasize that no pharmacological therapy is approved by the U.S. Food and Drug Administration (FDA) for treatment of psychopathology associated with dementia, meaning that clinicians must approach this clinical dilemma on a case-by-case basis.

A Rational Approach to Evaluation

Articulating a logical approach to evaluation and management of psychopathology in dementia, such as agitation or aggression, is by itself therapeutic because it offers reassurance to families and caregivers that a confusing situation can be clarified, understood, and helped. The approach proposed here, summarized in Figure 16–1, is an elaboration of prior work (Profenno et al. 2005; Rosenquist et al. 2000).

Nonpharmacological Interventions

Nonpharmacological interventions can include efforts to cue or reorient the person in a manner that is not frustrating, ensuring that the environment is comfortable and permits safe physical activity while providing visual cues, avoiding excessive stress or demands, maintaining a regular schedule of pleasant events, and optimizing interpersonal variables, such as by simplifying language, avoiding negative statements, and avoiding confrontation (Lyketsos et al. 2006). Cohen-Mansfield (2001) (see Table 16–1) offers an overview of approaches such as including music, pet therapy, massage, recordings of familiar persons' voices, walking programs, and the like. Most physicians are not accustomed to implementing these approaches, which do require a degree of familiarity and need to be tailored to each situation. It is therefore extremely helpful to partner with other specialists to assist in formulating a care plan and to learn how to formulate them more independently over time. The choice of collaborating health professional may vary depending on the community and the specific need; the options can include nurse specialists, social workers, selected psychologists or neuropsychologists, occupational therapists, speech therapists, or physical therapists. Psychiatrists historically have been good at functioning as members of an interdisciplinary team. Dementia care affords an ideal opportunity for this type of collaborative care. With practice, it can become a relatively easy process, with unexpectedly gratifying outcomes. Indeed, a marker of good disease management is involvement of these types of teams.

Pharmacological Interventions: General Precepts

For nonemergent problems in which nonpharmacological interventions have been exhausted, typically we adopt an approach that begins with a definition of a target symptom pattern at least roughly analogous to a drug-responsive syndrome. This has been termed the *psychobehavioral metaphor* (Leibovici and Tariot 1988). We then match the dominant target symptoms (the metaphor) to the most relevant drug class. This approach reflects most consensus guidelines (Alexopoulos et al. 2004; Doody et al. 2001; Small et al. 1997) but has not been established empirically.

We emphasize selection of a medication with at least some empirical evidence of efficacy and with the highest likelihood of tolerability and safety. We employ low doses and escalate slowly, assess target symptoms as well as toxicity, and discontinue the medication if it is harmful or ineffective. If a psychotropic is helpful at subtoxic doses, an empirical trial often is performed in reverse at the appropriate time and the patient monitored for recurrence of the problem. This type of approach is actually mandated in the nursing home setting in the United States by federal regulations created in 1987. Sometimes several medications need to be tried in series before a successful one is identified; sometimes combinations are warranted; sometimes no medication is found that is helpful.

Antipsychotic Medications

Within the context of the "metaphor" approach, antipsychotics would be used first for treatment of agitation with psychotic features. In reality, antipsychotics have been used and studied in patients with a wide range of psychopathology. There are two main classes of antipsychotics: so-called conventional antipsychotics and the newer atypical agents.

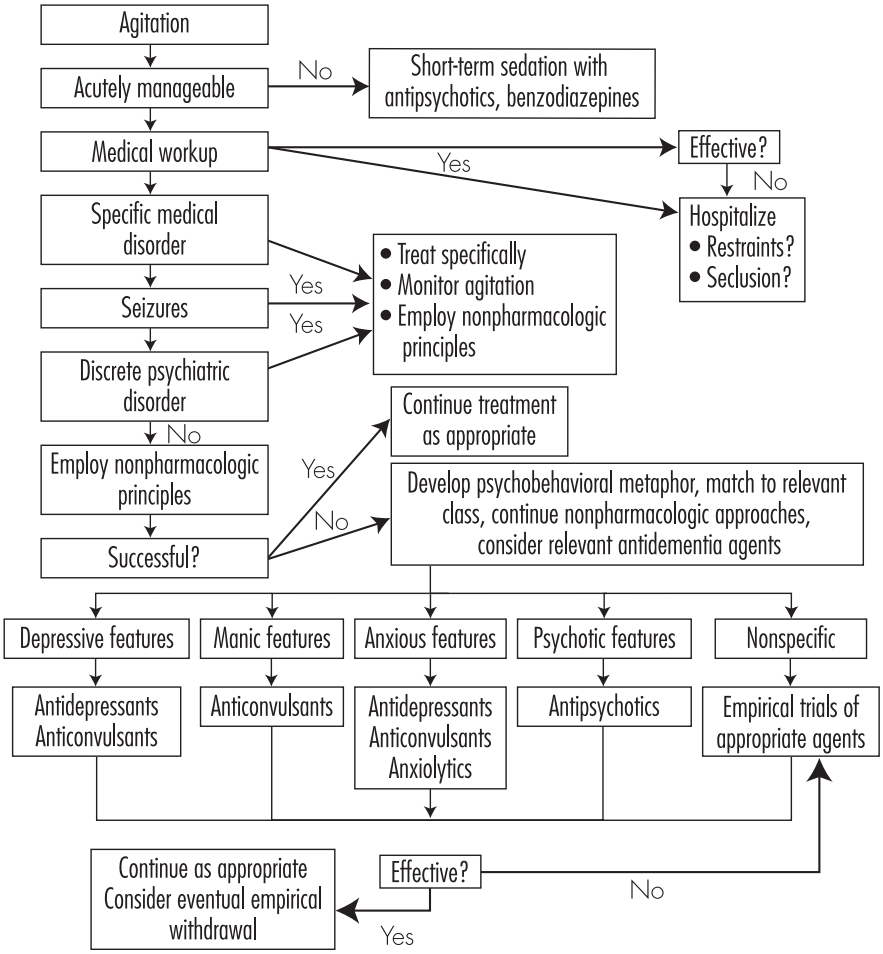

FIGURE 16–1. Management of agitation in dementia.
Source. Reprinted from Tariot PN: "Treatment of Agitation in Dementia." *Journal of Clinical Psychiatry* 60 (suppl 1):11–20, 1999. Used with permission.

Conventional Antipsychotics

Schneider et al. (1990) published a meta-analysis of clinical trials of conventional antipsychotics in patients with dementia, finding that, on average, 59% of patients treated with active medication showed categorical behavioral improvement versus 41% of those receiving placebo, an 18% drug-placebo difference, also referred to as the "treatment estimate." This treatment estimate tends to hold for most psychotropic agents.

Lanctôt et al. (1998) performed a more recent meta-analysis of studies of conventional agents and reported an average therapeutic effect (antipsychotic vs. placebo) of 26%, with placebo response rates ranging from 19% to 50%. Side effects were reported to occur more often on drug than placebo (mean difference, 25%). Side effects included akathisia, parkinsonism, tardive dyskinesia, sedation, peripheral and central anticholinergic effects, postural hypotension, cardiac conduction defects, and falls.

Lonergan et al. (2002) conducted a pooled analysis of five randomized trials of haloperidol versus placebo, which included two studies not incorporated in the above meta-analyses (Allain 2000; Devanand 1998), finding decreased aggression but not significant improvement in agitated symptoms overall among the haloperidol group. There also was a significant increase in adverse side effects, such as rigidity and bradykinesia, compared with placebo. Lonergan et al. concluded by recommending that haloperidol be used sparingly, on a case-by-case basis, with monitoring of side effects.

In view of the considerable toxicity of conventional agents, there was great hope that atypical antipsychotics would have special utility in patients with dementia (Alexopoulos et al. 2004b).

TABLE 16–1. Nonpharmacological management of neuropsychiatric symptoms

Environmental interventions
Behavioral management: differential reinforcement, stimulus control
Structured activities
Sensory enhancement: music, massage
Social contact: pets, one to one, family videos
Medical/nursing interventions: light therapy, hearing aids, pain management
Caregiver interventions
Staff training
Mental health care of caregiver
Day treatment
Exercise program
Respite care

Source. Reprinted from Cohen-Mansfield J: "Nonpharmacologic Interventions for Inappropriate Behaviors in Dementia: A Review, Summary, and Critique." *American Journal of Geriatric Psychiatry* 9:361–381, 2001. Used with permission.

Atypical Antipsychotics

Clozapine

Clozapine is the prototype atypical antipsychotic for the treatment of patients with schizophrenia, with arguably the lowest rate of motor toxicity and established efficacy in patients who are refractory to other therapies. However, there are no placebo-controlled trials in patients with dementia, only case series (Loy et al. 1999; Rosenquist et al. 2000; Tariot 1999). These series suggest a starting dosage of about 12.5 mg/day, with maintenance dosages of 12.5–50 mg/day. The limited literature emphasizes potential side effects such as sedation, ataxia, falls, delirium, and suppression of bone marrow function. Clozapine has a significant risk of agranulocytosis (about 1%), which is more common in the elderly than in younger patients, and regular monitoring of blood counts is required at least weekly for the first 6 months of continuous treatment, every other week for the following 6 months, and if blood counts remain acceptable, every 4 months thereafter. Other antipsychotics rarely may be associated with this adverse event, but routine monitoring of blood counts for this syndrome is not required for those drugs (Salzman et al. 1995). Clozapine has also been associated with an increased risk of diabetes and worsening lipid profiles in younger people; however, data are not available for elderly adults (American Diabetes Association et al. 2004). Of the atypical antipsychotics, clozapine is least associated with tardive dyskinesia, although rare reports of its development should be taken into consideration (Ertugrul and Demir 2005).

These toxicities, the need for monitoring of cell counts, and the lack of data indicating efficacy limit the utility of this agent in patients with dementia, although it does have a legitimate role in patients with movement disorders who have failed other agents (Parkinson Study Group 1999).

Risperidone

Risperidone has been studied more extensively than other psychotropic agents in this patient population. Preliminary studies explored a range of dosages (0.5–5 mg/day) that suggested that dosages of 0.5–2 mg/day might be tolerated best (Rosenquist et al. 2000). Three multicenter placebo-controlled trials have been conducted in nursing home patients. The first two were 3 months in duration and included patients with Alzheimer disease and/or vascular dementia who experienced agitation, psychotic features, or both. The first compared risperidone at dosages of 0.5, 1, and 2 mg/day with placebo in 625 subjects (Katz et al. 1999). Reasons for discontinuation included adverse events (15.4%), lack of efficacy (5%), and "other causes" (10.1%). Extrapyramidal features emerged in approximately 22% of subjects at the dosage of 2 mg/day, with a trend toward peripheral edema and dose-related sedation, and apparently good tolerability and safety otherwise. Using an a priori definition of clinical response, a 50% reduction in the total score of a behavioral rating scale, 33% of patients in the placebo group were rated as improved, a similar percentage of patients in the 0.5 mg/day group; 45% of those receiving 1 mg/day and 50% of patients receiving 2 mg/day were rated as improved. The treatment effects were statistically significant for the 1- and 2-mg/day dosages. Subscale scores indicated beneficial effects both on measures of psychosis as well as of verbal and physical aggression.

The second large nursing home trial compared placebo with flexible dosages (0.5–4 mg/day) of risperidone or haloperidol in 344 nursing home residents with dementia accompanied by agitation and/or psychosis (De Deyn et al. 1999). The mean dosages used were 1.2 and 1.1 mg/day, respectively. Eighteen percent of subjects dropped out of the trial because of adverse experiences, 15% because of lack of efficacy, and 6% for other reasons. There was no significant difference among the treatments on a global measure of psychopathology that was selected a priori. Secondary analyses showed an absence of effect of either active treatment relative to placebo on measures of psychosis, with a positive effect with both active treat-

ments on measures of aggression. Incidence of extrapyramidal adverse events was 11% for patients on placebo, 15% for those on risperidone, and 22% for those on haloperidol, numbers generally consistent with prior studies. Sedation occurred more frequently on haloperidol (18.3%) and risperidone (12.2%) than placebo (4.4%).

Brodaty et al. (2003) conducted a randomized, double-blind, placebo-controlled trial in elderly nursing-home patients with Alzheimer disease, vascular dementia, or a combination of these and significant aggressive behaviors. It is worth emphasizing the difference between behavioral inclusion criteria for this study (aggression) and the two previous studies (psychosis and/or agitation). In the Brodaty et al. (2003) study, 345 patients were randomized to receive a flexible dosage of either placebo or risperidone solution up to a maximum of 2 mg/day for 12 weeks. The mean dosage was 1 mg/day. Significant improvement in the group treated with risperidone was seen in the primary outcome measure, the Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield 1986), as well as a variety of secondary measures including the Clinical Global Impression of Severity (CGI-S) and of Change (CGI-C) scales (Guy 1976). Common adverse events were somnolence and urinary tract infection in risperidone-treated patients and agitation in placebo-treated patients.

A 2004 post hoc exploratory study of data from three randomized controlled trials of risperidone versus placebo in 1,150 nursing home residents, using the Korean version of the Cohen-Mansfield Agitation Inventory (CMAI-K) as a primary outcome measure, found risperidone to be significantly more effective in treating aggressive or psychotic behaviors like hitting, verbal repetition, scratching, restlessness, pacing, and wandering. The study found similar results using the Korean version of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD-K) (Reisberg et al. 1987); they found that risperidone was significantly more effective in treating physical threats and violence, agitation, and nonparanoid delusions (Rabinowitz et al. 2004).

Subsequent reviews yielded similar results. An 18-week randomized, double-blind, crossover comparison of risperidone and haloperidol in 120 Korean dementia patients with behavioral disturbances showed that risperidone had a favorable efficacy and tolerability profile (Suh et al. 2004). A 2006 post hoc analysis of this study found risperidone to be more effective than haloperidol in treating aggression on the BEHAVE-AD-K. Using the CMAI-K as a secondary measure, researchers also found that risperidone was significantly more effective in treating physical sexual advances, pacing, wandering, intentional falling, hoarding, verbal and physical repetition, and general negativism (Suh et al. 2006).

Risperidone has also been found effective for sleep disorders. In a study of 338 patients with dementia, Durán et al. (2005) found that patients and caregivers reported improvements in sleep, following 12 weeks of risperidone treatment. Compared with the baseline measure, total hours of sleep increased with risperidone (5.5 vs. 7.1 hours), whereas the number of hours awake at night decreased (1.2 vs. 2.3 hours). Rates of insomnia were also improved (40.1% vs. 8.4%), as were other sleep-related variables.

A conservative interpretation of the available evidence is that the efficacy of risperidone is roughly equivalent to that of haloperidol. The tolerability of risperidone appears to be better, with low-moderate risk of dose-related parkinsonism and sedation and numerically higher rates of peripheral edema in patients treated with risperidone versus placebo. As more data have emerged from the large clinical trials with risperidone, there has been more opportunity to examine possible side effects that might not be discernible in single clinical trials.

Olanzapine

An initial placebo-controlled parallel group study was conducted in 238 outpatients with dementia complicated by agitation, psychosis, or both. A flexible dosage of olanzapine in the 1–10 mg/day range was used, with an average dosage at the end of the trial of 2.7 mg/day. Neither toxicity nor efficacy were seen (Satterlee et al. 1995), leading to a follow-up study with fixed doses of olanzapine.

Street et al. (2000) reported on a 6-week, randomized, parallel group, multicenter study in 206 nursing home residents with dementia complicated by agitation, psychosis, or both, and who were treated with either placebo or olanzapine 5, 10, and 15 mg/day for 6 weeks. In patients receiving 5 and 10 mg/day, significant improvement compared with placebo was seen using a greater than 50% reduction from baseline in the sum of items for agitation/aggression, hallucinations, and delusions of the Neuropsychiatric Inventory: Nursing Home Version (NPI-NH) (Cummings et al. 1994; Wood et al. 2000). Patients receiving 5 mg/day also demonstrated significant improvement compared with placebo in broader assessments of psychopathology using total scores of the NPI-NH and the Brief Psychiatric Rating Scale (Overall and Gorham 1962). The article did not present global impression of change data. Sedation and postural instability were observed at all doses in at least 25% of subjects. Some of the patients from this trial received follow-up open-label, flexible-dose treatment for 18-week; results were consistent with the findings from the first article (Street et al. 2001).

Meehan et al. (2002) studied acute treatment of agitation with intramuscular olanzapine in 272 inpatients or nursing home residents with Alzheimer disease and/or

vascular dementia. Patients were given up to three injections of olanzapine at 2.5 mg or 5.0 mg, lorazepam 1.0 mg or 0.5 mg, or placebo, and assessed within a 24-hour period. Olanzapine was superior to placebo in treating agitation at 2 hours and 24 hours. Lorazepam was superior to placebo at 2 hours but not 24 hours. Adverse events were not significantly different between groups. At the time of this writing, this formulation has not been marketed.

De Deyn et al. (2004) randomized 652 patients with Alzheimer dementia with delusions or hallucinations to placebo or fixed-dose olanzapine (1.0, 2.5, 5.0, and 7.5 mg/day) in a 10-week double-blind study. There was significant improvement in the 7.5-mg olanzapine group compared with placebo on the NPI-NH Psychosis Total scores. On the CGI-C, the greatest improvement was seen in the 2.5-mg olanzapine group. The olanzapine groups had significant increases in weight, anorexia, and urinary incontinence, and no significant difference in extrapyramidal symptoms compared with placebo.

Quetiapine

A 1-year, open-label study of flexible-dose quetiapine was conducted in older patients with psychoses of multiple origins to explore dosing, safety, and tolerability, and to preliminarily address efficacy. The sample consisted of 151 subjects; 101 had either vascular dementia or probable Alzheimer disease (Tariot et al. 2000). The starting dosage was 25 mg/day, the range of dosages was 25–800 mg/day, and the median dosage at the end of the trial was roughly 100 mg/day. The study suggested possible benefit for agitation and/or psychosis in some patients, consistent with results from an open-label pilot study in outpatients with probable Alzheimer disease with psychosis or aggressive behaviors treated with quetiapine from 50–150 mg/day, showing decreased delusions and aggression on NPI scores (Cummings et al. 1994); performance on the Alzheimer's Disease Assessment Scale–Cognitive (Rosen 1984) did not change significantly (Scharre and Chang 2002).

Based on this pilot work, a 10-week multicenter placebo-controlled trial of quetiapine versus haloperidol was conducted in 284 elderly nursing home patients with psychosis that was operationally defined (Tariot et al. 2006). These criteria were implemented prior to the development of clinical criteria for the psychosis of Alzheimer disease proposed in 2000 (Jeste and Finkel 2000). Most subjects had dementia. This trial may have been the first large placebo-controlled study of an atypical antipsychotic in patients with dementia selected because of the presence of psychotic symptoms. Flexible doses of the medication were permitted; the mean daily dose of haloperidol was 2 mg at end point, whereas the mean daily dose of quetiapine was about 120 mg. None of the treatment groups differed with respect to reduction in measures of psychosis, which was the primary outcome of the trial. One of the secondary measures of agitation showed improvement with both the haloperidol and quetiapine treatment. Rates of somnolence were 25.3% for quetiapine, 36.2% for haloperidol, and 4.1% for placebo. Ten (11.0%), 15 (16.0%), and 12 (12.2%) participants in the quetiapine, haloperidol, and placebo groups, respectively, experienced adverse events rated as "serious." Parkinsonian features were most prevalent in the haloperidol group; other safety and tolerability measures differed little among groups.

This study led to a second placebo-controlled trial of quetiapine in 333 agitated nursing home residents with dementia (Zhong et al. 2007). This 10-week double-blind study randomized patients to a fixed-dose trial of quetiapine 100 or 200 mg/day. Titration was relatively rapid, achieving 100 mg/day by day 4 and 200 mg/day by day 8. Quetiapine at 200 mg/day was associated with significant improvement on a subscale of the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), the primary outcome, as well as several secondary outcomes; the 100-mg/day dose did not show significant improvement on the primary outcome. Incidents of cerebrovascular adverse events, postural hypotension, and falls were similar among groups. Mortality was numerically higher in the quetiapine group, although these mortality rates were not statistically different from placebo. The results of this study suggested that quetiapine 200 mg/day may be effective for treating agitation associated with dementia. However, results also emphasize that caution should be exercised, given concerns regarding increased mortality with atypical antipsychotics in this vulnerable patient population.

Ballard et al. (2005) performed a 26-week randomized, double-blind, placebo-controlled trial assessing quetiapine and rivastigmine in 93 institutionalized patients with dementia and severe agitation. Compared with placebo, neither group showed significant differences in improvement on the CMAI either at 6 or 26 weeks. Neither quetiapine nor rivastigmine was effective in the treatment of agitation in people with dementia in institutional care. Compared with placebo, quetiapine was associated with significantly greater cognitive decline, a result not found in the larger trials above (Tariot et al. 2006; Zhong et al. 2007).

Kurlan et al. (2007) conducted a randomized, double-blind, placebo-controlled clinical trial involving 40 patients with dementia, agitation, and parkinsonism and found that quetiapine (mean dosage 120 mg/day) was well-tolerated and did not worsen parkinsonism but did not show significant benefits for treating agitation or psychosis in patients with dementia and parkinsonism.

Ziprasidone

Ziprasidone is indicated for treatment of bipolar mania and schizophrenia, with minimal information about its use in people with dementia. Rocha et al. (2006) conducted a 7-week open-label trial involving 25 patients testing the effects of low-dose ziprasidone on agitation and other behavioral symptoms of dementia. By the end of the trial, only 15 patients remained; the main reasons for discontinuation were numerous adverse events, including somnolence, gastrointestinal symptoms, and parkinsonism. The mean total NPI score fell significantly from 47.1±17.1 (baseline) to 25.8±17.9, and the NPI score for caregiver burden showed significant improvement in distress. These limited data are insufficient to inform practice.

Aripiprazole

A 10-week placebo-controlled trial randomized 208 outpatients meeting clinical criteria for psychosis of Alzheimer disease (Jeste and Finkel 2000) to aripiprazole (De Deyn 2005). This was a flexible dose study, with doses ranging from 2–15 mg/day; the mean dose at end point was about 10 mg/day. Titration occurred slowly over a period of weeks. As is often the case with preliminary studies, the results were not fully informative. The primary outcome, the NPI Psychosis subscale, did not show a difference between drug and placebo, whereas there was a suggestion of behavioral benefit on some secondary measures. The medication was generally well tolerated, with numerically more frequent sedation in the active treatment group.

Two placebo-controlled studies of aripiprazole have been presented and/or published in abstract form, but not published at this point. The first was a placebo-controlled study of fixed-dose aripiprazole conducted in 587 nursing home residents with dementia and psychotic features (Breder et al. 2004). The only significant effect on measures of psychosis was found at the 10-mg/day dosage. Streim et al. (2004) performed the second placebo-controlled flexible-dose study, involving 256 nursing home residents with dementia. This study found no difference between a mean aripiprazole dosage of 8.6 mg/day and placebo. Details regarding safety and secondary measures from these studies are lacking.

Meta-Analysis of Atypical Antipsychotics

Individual trials are informative, but for purposes of this review, the meta-analysis of Schneider et al. (2006a) is quite helpful, particularly because it included results from both published and publicly presented unpublished placebo-controlled studies of atypical antipsychotics, the latter including trials that had been completed years ago but not published. These 15 trials were generally 6–12 weeks long and included participants with dementia of varying types complicated by agitation and/or aggression and/or psychosis; 3,353 received medication and 1,757 received placebo. The overall response rates on active treatment ranged from 48% to 65% versus 30% to 48% on placebo. On average, there was an incremental treatment benefit of about 18% for active drug over placebo. In other words, about one in five patients in these trials experienced significant improvement in symptoms. In this meta-analysis, atypical antipsychotics were about three times as likely as placebo to cause adverse events, the most common being somnolence, falls with and without injury, syncope, parkinsonism, bruising, peripheral edema, and infections. The weight gain and metabolic concerns with use of atypical agents in younger populations have not been seen in the relatively brief studies conducted thus far in the elderly.

This meta-analysis, which analyzed adverse events of atypical antipsychotic trials involving dementia patients, found that somnolence, falls, extrapyramidal effects, edema, and urinary tract infections were commonly reported. The analysis found that the risk was statistically greater with risperidone than the placebo. Specifically, 1.9% of those who received the atypical drug reported cases of cerebrovascular adverse events versus 0.9% on placebo. However, it is important to note that the noted significance in the risk increase of urinary tract infections was found only in the combined analysis, not in the individual studies. In a meta-analysis of nine placebo-controlled trials of atypical antipsychotic agents, Ballard and Waite (2006) found improved aggressive behavior with olanzapine versus placebo, but there was also a significantly higher rate of adverse effects, such as cerebrovascular events and extrapyramidal effects.

In a pooled analysis of five double-blind randomized trials, Lee et al. (2004) compared atypical antipsychotics with placebo in 1,570 patients, over 96% of whom were institutionalized and 76% of whom had been diagnosed with Alzheimer disease. The antipsychotics included risperidone, haloperidol, and olanzapine. Three trials found a statistically superior efficacy with the atypical antipsychotics versus placebo. Two trials comparing risperidone with haloperidol found no statistically significant difference in efficacy. Substantial adverse events were also recorded, including extrapyramidal symptoms and somnolence.

FDA Warning About Cerebrovascular Adverse Events and Increased Mortality

In October 2002, Health Canada issued a letter to health care professionals stating that risperidone use may be associated with cerebrovascular adverse events in elderly patients with dementia (Wooltorton 2002). This notification was based on the observation of an increased incidence of cerebrovascular events in patients with dementia in four placebo-controlled trials of risperidone. The data revealed that 4% (29/764) of risperidone-treated patients versus 2% (7/466) of placebo-treated patients had a cerebrovascular adverse event, defined as either a transient ischemic attack or stroke, including four deaths among risperidone-treated patients and one among placebo-treated patients. The effect was seen in only two of the four studies.

In April 2003, the FDA issued a similar warning of cerebrovascular events with risperidone in patients with dementia and noted that risperidone has not been shown to be safe or effective in treating dementia-related psychosis (U.S. Food and Drug Administration 2003). Studies have shown evidence for an increase of cerebrovascular events in relation to three second-generation atypical antipsychotics (aripiprazole, olanzapine, and risperidone). In 2004, Eli Lilly released a warning of increased risk of cerebrovascular events in dementia patients treated with olanzapine. They found the incidence in olanzapine (1.3%) to be triple that of the placebo (0.4%), with a concomitant increase in mortality (3.5% vs. 1.5%) (U.S. Food and Drug Administration 2004).

In placebo-controlled trials with aripiprazole in psychosis of Alzheimer disease (two flexible-dose trials and one fixed-dose study), there was an increased incidence of stroke and transient ischemic attack, including fatalities, in aripiprazole-treated patients whose mean age was 84 years (range=78–88 years) (Abilify prescribing information 2008). Although not directly reported in the prescribing information, data from a "Dear Doctor" letter from Bristol-Myers Squibb (2005) indicated that cerebrovascular events occurred in 1.3% of aripiprazole-treated patients versus in 0.6% of placebo-treated patients (relative risk, 2.3; 95% confidence interval, 0.5–10.3). In the fixed-dose study, there was a statistically significant dose-response relationship for cerebrovascular events in patients treated with aripiprazole.

Data on quetiapine use for dementia patients are somewhat limited compared with risperidone, olanzapine, or aripiprazole. There is no specific warning. However, Schneider et al. (2005) performed a meta-analysis of pooled data from 15 randomized trials and found that the rates of cerebrovascular adverse events were 1.9% with atypical antipsychotics versus 0.9% with placebo. These data produced an odds ratio of 2:1.

These warnings were later extended. The FDA reviewed 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone, and quetiapine in 5,106 elderly demented patients with behavioral disorders. A 1.6- to 1.7-fold increase in all-cause mortality rate was found. Specific causes of these deaths were heart-related events (e.g., heart failure, sudden death) or infections (mostly pneumonia). In 2005, the FDA requested that the producers of olanzapine, aripiprazole, risperidone, quetiapine, clozapine, and ziprasidone "black box" these medications, requiring warnings of risks to be placed on packaging (U.S. Food and Drug Administration 2005). These results are consistent with the meta-analysis by Schneider et al. (2005) of randomized, placebo-controlled trials of aripiprazole, olanzapine, quetiapine, and risperidone in 3,353 patients (603 to aripiprazole, 1,184 to olanzapine, 391 to quetiapine, 1,175 to risperidone, and 1,757 to placebo). The overall death rate was 3.5% for atypical antipsychotics versus 2.3% for the placebo, with a relative risk of 1.65.

Recent studies have shed further light on the possible link between atypical antipsychotics and increased mortality and cerebrovascular events, and also addressed the question of conventional agents. Hermann et al. (2004), in a population-based retrospective cohort study of 13,318 persons, failed to show a significant increase in the risk of stroke among patients receiving olanzapine or risperidone when compared with those initiating therapy with typical antipsychotics. Hermann and Lanctôt (2005) conducted post hoc analyses of pooled data from 11 randomized controlled trials of risperidone and olanzapine in dementia patients. They found an increased risk of cerebrovascular adverse events in those taking atypical antipsychotics compared with placebo, but they did add that some of the risk could be attributed to nonspecific events unrelated to strokes. Schneider et al. (2006c), in a meta-analysis of atypical antipsychotic trials involving dementia patients, found that among the 3,327 patients who received atypical antipsychotics, 1.9% (63) reported cerebrovascular adverse events versus 0.9% (16 events) in the 1,728 patients on placebo.

Johnson and Johnson Pharmaceutical Research and Development collected data from six phase 2 and 3 double-blind trials in the elderly that analyzed the mortality of risperidone versus placebo in 1,721 patients. The mortality for risperidone was 4.0% versus 3.1% with placebo from trial initiation to within 30 days after discontinuation. No significant relationship was found between risperidone dosage and mortality. In each trial, common adverse events associated with mortality were pneumonia, cardiac failure, and cerebrovascular disorder. Overall, there was a nonsignificant increase in mortality during treatment with

risperidone. Such inconclusive data have been echoed in numerous other studies (Haupt et al. 2006).

In a population-based retrospective cohort study, Gill et al. (2005) evaluated the risk of stroke in 32,710 older Ontario adults with dementia (65 years); 17,845 received an atypical antipsychotic and 14,865 received a typical antipsychotic. The main outcome measure was admission to the hospital from an ischemic stroke. Participants receiving atypical antipsychotics showed no statistically significant increased risk of ischemic stroke compared with those receiving conventional antipsychotics (adjusted hazard ratio 1.01, 95% confidence interval 0.81 to 1.26). This finding was consistent in subgroup analyses of individual atypical antipsychotic drugs (risperidone, olanzapine, and quetiapine).

Raivio et al. (2007) assessed the impact of atypical and conventional antipsychotics on mortality. A total of 254 elderly Finnish institutionalized patients with dementia were followed for 2 years. Nearly half (48.4%) of this population received antipsychotic medication (37.4% received conventional antipsychotics and 11% received atypical antipsychotics). The mean number of hospital admissions was higher among those who did not receive any antipsychotic medication. The use of atypical antipsychotics (risperidone, olanzapine) showed a lower risk of mortality (32.1%) compared with conventional antipsychotics (45.3%) and those who did not receive any neuroleptic (49.6%). Therefore, neither the use of conventional or atypical antipsychotics was found to increase mortality.

These warnings should be interpreted cautiously. No agent has been subjected to the extensive testing that risperidone has, meaning that uncommon adverse events are more likely to be seen in the risperidone literature. Further, close inspection of the data suggests the possibility that patients with cerebrovascular disease might be the most susceptible to cerebrovascular adverse events. This cannot be definitively addressed because the studies were not designed to assess side effects or efficacy as a function of baseline medical condition. The fact that deaths seem to occur for so many different reasons suggests that any type of medication-induced impairment in this population, including sedation, incoordination, dysphagia leading to aspiration, and falls, could contribute to tipping the scales from vulnerability to death.

The Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease

The Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) study randomized 421 outpatients with Alzheimer disease and symptoms of psychosis and/or aggression to treatment with risperidone, olanzapine, and quetiapine. Conventional antipsychotic agents were not included in the CATIE-AD trial because the risk of side effects in this population was considered to be excessive. Phase 1 study results have been published (Schneider et al. 2006b). The primary measure of effectiveness, time to discontinuation for any reason, was not significantly different between the treatment conditions, with median treatment durations of 8.1 weeks for olanzapine, 5.3 weeks for quetiapine, 7.4 weeks for risperidone, and 8.0 weeks for placebo. The median time to discontinuation because of lack of efficacy was significantly longer with olanzapine and risperidone (22.1 and 26.7 weeks, respectively) versus quetiapine and placebo (9.1 and 9.0 weeks, respectively). Safety findings were generally consistent with reports of prior studies. However, the atypical antipsychotics were associated with a shorter time to discontinuation because of adverse events or drug intolerability compared with placebo. Time to discontinuation because of intolerability favored placebo and quetiapine. Overall, intolerability accounted for discontinuations in 24% of patients receiving olanzapine, 16% receiving quetiapine, 18% receiving risperidone, and 5% receiving placebo. The trial showed that a minority of patients can show clinical benefit without toxicity.

Summary

Individualized assessment of the risk/benefit ratio is necessary when considering whether to treat with an antipsychotic. The risk of not treating a morbid complication of the illness has to be weighed against the perceived or real risks of active treatment, ranging from a relatively high likelihood of sedation with most antipsychotics to a low possible risk of cerebrovascular adverse events or death. Furthermore, if medication treatment is deemed necessary, and an alternative agent is to be considered, how convincing are the data about its safety *and* efficacy?

Antidepressants

Trazodone

Case series and open trials suggest benefit of trazodone in dosages from 50 mg/day to 400 mg/day (Rosenquist et. al. 2000). Symptoms of irritability, anxiety, restlessness, and depressed affect have been reported to improve in some cases, along with disturbed sleep, with side effects of sedation, orthostatic hypotension, and occasional delirium. Sultzer et al. (1997) compared trazodone at a mean dosage of 220 mg/day with haloperidol at a mean dosage of

2.5 mg/day in 28 patients in a 9-week crossover study. Agitation improved equally in both groups, with better tolerability in the trazodone group. Teri et al. (2000) reported negative results for all active treatments in a multicenter outpatient study contrasting trazodone, haloperidol, placebo, and caregiver training. The available evidence is an example of clinical equipoise, with limited positive and more extensive negative evidence for efficacy. A prior Expert Consensus Guideline (Alexopoulos et al. 2004a) favored use of trazodone primarily to treat sleep disturbance, relegating it to second- or third-line use for "mild" agitation. A typical starting dosage would be 25 mg/day, with maximum dosages usually of 100–250 mg/day.

Selective Serotonin Reuptake Inhibitors

There are mixed results in clinical trials of selective serotonin reuptake inhibitors for agitation in patients with dementia. Nyth and Gottfries (1990) performed a review of controlled studies of citalopram in patients with various dementia diagnoses, which suggested some beneficial behavioral effects. This conclusion was supported by two open trials of this agent (Pollock et al. 1997; Ragneskog et al. 1996). Using a randomized, double-blind study, Karlsson et al. (2000) compared citalopram and mianserin in efficacy and tolerability in 336 patients with or without dementia. Using the Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg 1979) as their primary measure, both medications were equally effective in treating depression in dementia patients. These agents showed high tolerability with few adverse effects, including fatigue, somnolence, and insomnia. Based on their data, the authors recommended citalopram as an effective, well-tolerated treatment for depression in patients with or without dementia.

A double-blind, placebo-controlled study compared citalopram and perphenazine with placebo in patients with various dementia diagnoses (probable Alzheimer disease and dementia with Lewy bodies being the more common diagnoses) who had at least one symptom of psychosis or behavioral disturbance (Pollock et al. 2002). Hospitalized patients (N=85) were treated after 3 days of dose escalation with dosages of 20 mg/day citalopram or 0.1 mg/kg/day of perphenazine for up to 14 days. Both citalopram and perphenazine demonstrated significant improvement compared with placebo on Neurobehavioral Rating Scale (Levin et al. 1987) scores for the agitation, lability, and psychosis. Side effects were similar in the three treatment groups.

Pollock et al. (2007) tested the efficacy of citalopram versus risperidone in treatment of psychosis and agitation in patients with dementia. A total of 103 dementia patients who were hospitalized because of behavioral symptoms were randomized in this 12-week study. There was no statistical difference between citalopram and risperidone on the primary behavioral outcome measure, the NPI; agitation and psychotic symptoms decreased in both treatment groups. There were significantly greater side effects with risperidone than with citalopram, especially sedation. Comparable increases in extrapyramidal symptoms were seen in the two groups.

In a review of 29 double-blind, placebo-controlled, randomized trials, Sink et al. (2005) found that among five trials of antidepressants, only one study of citalopram showed improvement in neuropsychiatric symptoms other than depression in dementia patients.

No benefit has been reported for fluoxetine or fluvoxamine, whereas only anecdotes are available regarding other serotonergic agents (Loy et al. 1999). In an open case series, 15 patients living in nursing homes or in the community with Alzheimer disease or vascular dementia were treated with paroxetine 10–40 mg/day for 3 months. All patients demonstrated improvement in verbal agitation on the CMAI (Cohen-Mansfield 1986; Ramadan et al. 2000).

Serotonergic agents are used quite widely despite the relative lack of clinical trials data regarding their effectiveness. This may be because of familiarity with this class of agents for treatment of depressive disorders as well as basic, preclinical, and clinical evidence linking impulsivity to disordered serotonergic function (Coccaro 1996). The side effect profile of this class includes gastrointestinal symptoms, sedation or insomnia, sexual dysfunction, hyponatremia, and occasional neuromuscular signs, with rare anecdotes of paradoxical agitation.

Benzodiazepines

Most studies are older, were conducted in ill-defined populations, were usually not placebo-controlled, and tended to demonstrate an average reduction in agitation with short-term therapy (Loy et al. 1999). A study by Coccaro et al. (1990) was the most methodologically rigorous study. Oxazepam 10–60 mg/day was compared with low-dose haloperidol in patients with mixed dementia diagnoses. Five percent of patients in the benzodiazepine group improved versus 24% of those in the haloperidol group. In a study comparing alprazolam 0.5 mg two times a day with haloperidol 0.6 mg/day in a crossover study (Christensen and Benfield 1998), the doses of both agents were probably too low to produce an effect, and none was seen. A randomized, double-blind controlled trial com-

paring intramuscular lorazepam with intramuscular olanzapine in 331 patients showed that lorazepam was equal to olanzapine in efficacy at 2 hours but inferior at 24 hours (Meehan et al. 2002). However, at this time, no studies have compared benzodiazepines with each other nor are there any data concerning their efficacy after 8 weeks.

It has been suggested that, in comparison to antipsychotics, benzodiazepines may have more side effects and a lower likelihood of benefit (Cevera 1974; Christensen and Benfield 1998; Coccaro et al. 1990; Covington 1975; Kirven and Montero 1973; Meehan et al. 2002; Stotsky 1984). Side effects associated with benzodiazepines include ataxia, falls, confusion, anterograde amnesia, and sedation. Benzodiazepines are not recommended beyond a brief period of use because of risks of potential dependence, tolerance, sedation, insomnia, cognition deterioration, disinhibition, and delirium (Patel and Tariot 1995). These agents have also been associated with respiratory suppression during sleep.

For these reasons, use of benzodiazepines typically is limited to agitation associated with procedures or time-limited acute or as-needed use, with chronic use only in those patients for whom other agents have proven ineffective. Benzodiazepines are recommended for use with only minimum effective doses, given that side effects are dose related. Also, because of withdrawal risks, agents that are prescribed for an extended period should not be stopped abruptly but tapered. Drugs with simpler metabolism and relatively short half-lives, such as lorazepam 0.5 mg one to four times daily, are selected most often; long-acting agents such as diazepam, clonazepam, flurazepam, and nitrazepam are generally avoided. In elderly patients, agents such as clonazepam with long half-lives and long-lived metabolites may take up to several weeks to reach steady levels and therefore generally are not recommended.

Buspirone

Buspirone treatment for dementia patients has been reported only in case series and small clinical trials (Colenda 1988; Cooper 2003; Herrmann and Eryavec 1993; Sakauye et al. 1993; Tiller et al. 1988). An 8-week single-blind, placebo-controlled study found improvement in measures of aggression, although only 12 of the 20 subjects completed the study (Levy et al. 1994). Lawlor et al. (1994) conducted a crossover study in 10 subjects comparing buspirone with trazodone, finding no relative benefit of buspirone. Cantillon et al. (1996) compared buspirone 15 mg/day with haloperidol 1.3 mg/day for 10 weeks in 26 subjects, finding no significant benefit of either drug. The medication requires twice daily dosing, is generally well tolerated, and can require several weeks to achieve maximal clinical benefit. The level of evidence supporting use of this agent is very weak. Consensus statements (e.g., Alexopoulos et al. 2004a) suggest a possible role for patients with mild agitation associated with anxiety or irritability, starting at 5 mg two times a day and increasing to a potential maximum daily dose of 40–60 mg.

Anticonvulsants

Carbamazepine

Chambers et al. (1982) performed an 8-week crossover study of carbamazepine in 19 women with mild agitation who also received antipsychotics: this brief report was negative. Tariot et al. (1994, 1995) performed a 12-week placebo-controlled pilot crossover study in 25 patients, showing encouraging effects on agitation and not other aspects of psychopathology and suggesting good tolerability. A placebo-controlled study of 6 weeks' duration in 51 patients also found a significant reduction in agitation using a mean dosage of 300 mg/day (Tariot et al. 1998). Tolerability in these studies was generally good, with evidence of sedation and ataxia; 8% of subjects dropped out because of side effects in the larger confirmatory carbamazepine study. A 6-week, placebo-controlled, parallel group trial of carbamazepine 400 mg/day in 21 patients with probable Alzheimer disease with agitation who had failed previous treatment with antipsychotics reported improvement in a secondary outcome (Olin et al. 2001). Side effects seen in other populations, such as rashes, sedation, hematological abnormalities, hepatic dysfunction, and altered electrolytes, would be more likely with widespread use of carbamazepine in the elderly. Further, it has considerable potential for significant drug-drug interactions. The carbamazepine studies provide evidence to support the concept that anticonvulsants have anti-agitation efficacy. Whether alternative agents may be equally or more effective, or at least safer and better tolerated, remains an open question.

Valproic Acid

Also known generically as valproate, and available as the acid as well as the enteric-coated derivative, divalproex sodium, valproic acid is approved by the FDA for treatment of acute mania associated with bipolar disorder. The first placebo-controlled study of this agent for agitation in dementia was 6 weeks in duration (Porsteinsson et al.

2001). Divalproex sodium at a mean dosage of 826 mg/day (mean level 46 μg/dL) was assessed in 56 nursing home residents with dementia complicated by agitation. The purpose of this study was to establish the effect size, safety, and tolerability and to clarify proper titration and dosing in order to plan a larger study. The primary measure of agitation did not show benefit, but there was a sufficient trend to warrant proceeding to a larger trial. Serious adverse events occurred at a rate of 10% in both the drug and placebo groups; milder side effects occurred more frequently in the drug group, chiefly consisting of sedation, gastrointestinal distress, and ataxia, typically rated as mild, and the expected decrease in average platelet count (about 20,000/mm^3).

A multicenter, randomized, placebo-controlled, 6-week, study of divalproex sodium conducted in 172 nursing home residents with dementia and agitation who also met criteria for secondary mania incorporated a rapid dosing and titration protocol resulting in a target dosage of 20 mg/kg/day 10 days (Tariot et al. 2001). This titration rate and dosage resulted in sedation in about 20% of the drug-treated group and a relatively high dropout rate, leading to premature discontinuation of the study (completers, n=100). There were no significant drug-placebo differences in manic features, but there was a significant effect of drug on agitation. Sedation occurred in 36% of the drug group versus 20% of the placebo group, and mild thrombocytopenia occurred in 7% of the drug group and none of the placebo-treated patients.

A multicenter, 6-week, placebo-controlled trial was conducted by the Alzheimer's Disease Cooperative Study in 153 nursing home residents with dementia who were agitated (Tariot et al. 2005). No drug-placebo difference was seen in any behavioral measures, using an average dosage of about 750 mg/day. Side effects were as previously described. Finally, a randomized, double-blind, placebo-controlled, crossover study of valproate 480 mg/day for 3 weeks was conducted in patients with dementia and aggressive behavior (Sival et al. 2002). No significant impact on aggressive behavior was seen according to the primary outcome measure, whereas there was a trend toward improvement in measures of aggression as well as trends for improvement for dependent and suspicious behaviors. There were no drug-placebo differences in rate or type of adverse events.

The results from one of these trials (Tariot et al. 2001) were used to amend the package insert information, cautioning against use of similar dosages (20 mg/day) and/or titration rates in the elderly. If valproate is used, the available evidence suggests a starting dosage of about 125 mg, orally, two times a day, increasing by 125–250 mg increments every 5–7 days, with a maximal dosage determined by clinical response, or where there is uncertainty, a serum level of about 60–90 μg/mL. In our hands, the typical target dosage is about 10–12 mg/kg/day. The utility of the new once-daily extended-release formulation is not established in this population, although one preliminary study suggested reasonable tolerability (Profenno et al. 2005).

There are no controlled studies of which we are aware of the newer anticonvulsants, including lamotrogine, gabapentin, and topiramate. Emerging biological data addressing the mechanism of action of mood stabilizers suggest in particular that lithium and valproate but not other agents may have clinically relevant neuroprotective properties (Tariot et al. 2002). The possibility of secondary prevention of psychopathology by administration of valproate is being addressed in a multicenter trial being conducted by the Alzheimer's Disease Cooperative Study (Tariot et al. 2002). In the meantime, consensus statements suggest a limited role for anticovulsants in view of the limited and mixed evidence regarding efficacy and safety (Alexopoulos et al. 2004a).

Antidementia Therapies

The clinical use of antidementia agents is addressed in Chapter 18 of this volume, "Pharmacological Treatment of Alzheimer Disease and Mild Cognitive Impairment," but it is important to note that they can play an important role in the medical treatment of psychopathology associated with dementia. The evidence from clinical trials addressing their efficacy comes primarily from secondary analyses of behavioral outcomes because there are few trials prospectively assessing behavioral efficacy of these agents. It is clinically appropriate to consider a treatment trial of a cholinesterase inhibitor and/or memantine at some point in treating most patients with Alzheimer disease because these medications are quite safe and they may show some relief of, or delay emergence of, psychopathology. Therefore, we use them routinely to try to mitigate such psychopathology.

Conclusion

Clinical trials in this patient group show that the overall treatment effect for drugs that "work" is about 20%, which is nearly the same rate as the likelihood of significant side effects. Some patients can be helped without being harmed, some gain no benefit, and some are only harmed. Clinicians should be familiar with evidence addressing ef-

ficacy and toxicity of available treatments; determine whether a particular treatment is justified, including explicitly assessing degree of subjective distress, functional impairment, dangerous resistance to personal care, or risk of harm to self or others; and evaluate the patient's risk profile in view of the treatment that is being considered. Whether the risks and benefits warrant use of a particular treatment is a judgment that needs to be made on a case-by-case basis. This justification should be explained to the relevant stakeholders and documented accordingly. The patient should be monitored thoughtfully so that treatment that is ineffective or harmful can be stopped. Given the relatively low likelihood of achieving benefit without harm in using medication, it is important to use nonpharmacological interventions as thoughtfully and consistently as possible.

KEY POINTS

- Behavioral and psychological disturbances require thoughtful appreciation of their phenomenology, assessment, and management.
- Best practice precepts emphasize careful clinical evaluation and dementia diagnosis, assessing for pain and delirium, and employing nonpharmacological approaches first.
- Pharmacological therapy is guided by the "psychobehavioral metaphor": define a target symptom pattern analogous to a drug-responsive syndrome and then match the dominant target symptoms to the most relevant drug class.
- Employ low doses, escalate slowly, assess target symptoms and toxicity, and discontinue medication if harmful or ineffective.
- There is a benefit of about 18% for atypical antipsychotics over placebo (about one in five patients experience significant improvement).
- Use of atypical antipsychotics is associated with slightly increased risk for cerebrovascular adverse events and all-cause mortality.
- In considering whether to use an antipsychotic, weigh the risk of not treating a morbid complication of the illness against the risks of active treatment.
- Evidence for efficacy and lack of toxicity is largely lacking or inconclusive for nonantipsychotic psychotropics.
- Antidementia therapies, which are clinically appropriate in the treatment of Alzheimer disease, may benefit behavioral features.

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CHAPTER 17

Behavioral and Environmental Management

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Behavioral and environmental management is one element of a comprehensive approach to persons with dementia and their caregivers. Behavioral and environmental interventions address symptoms and situations that arise at all stages of dementia progression. Chapter 19 of this book deals specifically with the management of persons with late-stage dementia.

Theoretical Underpinnings

The most influential theoretical contribution to these efforts has been the work of Lawton and colleagues. Lawton's ecological model of the interaction between the environment and the individual (Lawton and Nahemow 1973; Lawton and Simon 1968) laid the groundwork for exploration of person–environment fit. Lawton and Nahemow's Competence Press Model (Lawton and Nahemow 1973; Nahemow 2000) holds that the individual's ability to interact successfully with the demands of the environment decreases as the individual declines cognitively. As cognitive and functional ability are reduced with disease progression, persons experience stress because they are less able to control their environment. Matching an individual's level of function with the demands of the environment engenders emotional comfort and fosters independence in performance of daily care tasks. This increasing importance of the environment on the individual with dementia was termed *the docility hypothesis* (Lawton and Nahemow 1973). Lawton posited that the physical environment serves a maintenance function, a stimulation function, and a supportive function in the interplay between persons and their surroundings. Because persons with dementia are no longer able to adapt to the demands of their environment, modifications to the environment are necessary to restore balance between environmental press and the individual's ability to manage environmental

demands. Alternative models regarding the interplay between the environment and individuals with dementia have been proposed and include the Progressively Lowered Stress Threshold (PLST) model (Hall and Buckwalter 1987) and the Need-Driven, Dementia-Compromised Behavior (NDB) model (Algase et al. 1996). The PLST model suggests that greater cognitive impairment results in progressively lower thresholds for stress. In the NDB model (Algase et al. 1996; Kovach et al. 2005), the person with dementia is seen as pursuing personal goals or needs but lacking the ability to express these needs effectively. This model has been applied in the serial assessment of resident pain within nursing home settings (Kovach et al. 1999). We believe that Lawton and colleagues' model has greater utility than the other two models because it also suggests that too little environmental stimulation can result in poor person–environment fit.

Cohen-Mansfield (2003) has developed a model that considers multiple individuals and systems as contributing to the goals of treatment for individuals with dementia and the means by which conflicts of interest between stakeholders might be resolved. Her model includes the person with dementia, the caregivers (family, staff, care team), the physical environment, and systems including policies and administrative issues. Like Lawton, Cohen-Mansfield suggested matching the intervention or treatment plan to the individual or aspect of the physical or social environment that is most likely to promote change in the target behavior of the patient. Cohen-Mansfield (2005) also underscores the importance of weighing the well-being of the patient with dementia over the convenience of the caregiver. Too frequently, the autonomy and comfort of the patient are compromised in favor of speed or uniformity of care in a nursing home setting, which tends to exacerbate dependence and behavioral problems (Baltes 1988; Woods 1999). Cohen-Mansfield takes the approach that comfort and positive life experiences are more relevant for persons with dementia than experiencing reality that is consistent with caregivers' points of view.

Many suggestions have been made for designing customized environments for individuals with dementia. Having a framework for understanding the genesis of behavior problems is useful in the design of therapeutic environments. One such framework views behaviors in terms of their antecedents and consequences, aiming to modify triggers and to reinforce adaptive behaviors. These ABCs (antecedent, behavior, consequence) of behavior management may entail modifying the physical or social environment. In the realm of the physical environment, for example, decreased visual acuity and low lighting have been associated with decreased calorie consumption (Brush et al. 2002). By identifying the antecedent (poor lighting) and making modifications to the physical environment, the problem behavior of poor independent eating habits is modified. As a consequence, nutrition is improved. In the realm of the social environment, decreases in social engagement have been associated with withdrawal, depression, and agitation (Kolanowski et al. 2006). Providing activities such as memory books including pictures of patients' early and present lives has been shown to improve social engagement and decrease agitation (Bourgeois et al. 1997; Burgio et al. 2001).

Understanding Dementia

Sensory Loss

All perceptual systems can be affected by dementing illnesses. Bakker (2003) argues that sensory loss is a critical factor that leads to increased impairment and confusion in dementia patients. For individuals with memory and information-processing deficits, reliance on compensatory sensory modalities becomes increasingly important. However, as problems with visuospatial function, depth perception, glare, and visual acuity increase, individuals may have increasing difficulty orienting themselves in their environment or recognizing previously familiar sights. In addition to exacerbating symptoms of dementia, sensory losses can also mimic deficits that the individual may not yet have developed. For example, an inability to read signs due to poor lighting (e.g., "Dining Hall," "Restroom") may be misperceived as disorientation or difficulty with finding one's way (Calkins 2001).

Similarly, misperception of auditory stimuli also increases as the aphasias associated with progressive dementia worsen. The sound of rain may be misperceived as footsteps in the hall, or a beeping alarm clock may be confused with a telephone ringing or fire alarm sounding. Although individuals with dementia may not experience decreases in sensitivity to touch beyond the effects of normal aging, uninvited or unannounced touch by others may be upsetting. Unlike tactile sensations, changes in olfaction are often affected by dementia progression. Luzzi et al. (2007) compared the ability to distinguish olfactory stimuli among individuals in the early stage of four different types of dementia: Alzheimer disease, semantic dementia, frontotemporal dementia, and corticobasal degeneration. There were slightly different patterns of identification across different types of dementia. Individuals with Alzheimer disease showed the poorest performance across odor-naming tasks, probably because of damage to the hippocampal formation and the entorhinal

cortex. There is also loss of taste in normal aging and in Alzheimer and Parkinson disease (Lang et al. 2006).

Discomfort and Pain

Conditions that produce pain and discomfort are very common in persons with dementia; these include arthritis, vertebral compression fractures, bed sores, urinary tract infections, and neuropathies in addition to the pain and discomfort of prolonged immobility (Shega et al. 2004; Williams et al. 2005). Demented patients with painful conditions frequently receive inadequate treatment (Allen et al. 2003b; Fisher et al. 2002). Detection of pain usually relies on self-report, but in patients whose capacity to communicate is impaired, clinicians must rely on behavioral observation (Buffum et al. 2007; Snow and Shuster 2006). Manifestations of discomfort include distressed facial expressions, vocalizations, disturbed mood, and agitation or behavioral disturbance. The assessment of pain among individuals with dementia is complicated by the overlap of observable behaviors that may indicate either physical discomfort or behavioral and psychological symptoms related primarily to dementia.

Cognitive and Functional Symptoms

Changes in attention and recent memory are the most prominent symptoms of early decline in Alzheimer disease. Some individuals may compensate for decreasing cognitive abilities by increasing reliance on close loved ones or on lists and other environmental cues. Having a place for everything and having everything in its place best summarizes what is needed to avoid losing objects around the house. Later, these cues do not suffice and must be replaced with simplification of environmental demands, such as escorting individuals to the dining table instead of encouraging them to remember when and where they eat.

Behavioral and Psychological Symptoms

Psychological and behavioral manifestations are part of the dementia syndrome (see Chapter 15 of this book, "Psychiatric Disorders in People With Dementia," for an extensive review). Behavioral manifestations of dementia make care tasks more difficult for family and professional caregivers and affect quality of life and social interactions (Allen et al. 2003a; Burgio et al. 2001). Many individuals with moderate to severe dementia develop significant behavior problems (Burgio et al. 2007). These problems may be conceived of as *behavioral excesses,* in which the occurrence of a behavior is the problem (e.g., hitting, wandering, restlessness, screaming), or *behavioral deficits,* in which the nonoccurrence of the behavior is the problem (e.g., withdrawal, apathy) (Allen-Burge et al. 1999). Internal stimuli or stimuli in the physical or social environment may elicit behavioral and psychological symptoms of dementia, and their expression may vary over time and course of the disease (Burgio et al. 2007).

Depression, anxiety, apathy, and withdrawal are all common. Anxiety is often accompanied by suspiciousness, which may manifest in hiding and hoarding behaviors. Various forms of agitation are exhibited by a majority of persons with dementia (Ballard et al. 2002; Cohen-Mansfield et al. 1995). Hallucinations and delusional beliefs can be troublesome. Removing mirrors from rooms of individuals with dementia may reduce agitated behavior because of patients seeing themselves as strangers or intruders (Cohen-Mansfield 2005). If, on the other hand, delusions or hallucinations are comforting, as when individuals with dementia talk with deceased relatives, the best intervention is to inform caregivers that these symptoms serve a positive function and should be accepted rather than challenged.

Environmental Issues and Assessment of Fit

As predicted by the maintenance, stimulation, and support functions of the environment in Lawton and Nahemow's Competence Press model, modifications to the home environment have been shown to facilitate adaptive behaviors on the part of persons with dementia (Calkins 2004). Home modifications include grab bars, ramps, roll-in showers, and wide doorways. Assistive devices include toilet seat risers, reachers, and walkers. Brawley (2001) has made several environmental design recommendations for incorporating gardens and other outdoor spaces into environments for individuals with dementia with the goal of improving quality of life. Creating level walkways using materials that are dark, high contrast, and slip-resistant helps to reduce glare, increase mobility, prevent falls, and promote safe activity. Brawley also describes the Alzheimer's Garden Project, a joint venture between the Alzheimer's Association and the American Society of Landscape Architects. Among the project's many goals is to provide a sense of purpose and promote well-being through involvement in gardening activities. Similarly, Chalfont and Rodiek (2005) noted the importance of investment in outdoor spaces in nursing homes to facilitate better sleep and to de-

crease agitation and aggression by allowing physical activity. They proposed blurring the boundary between indoors and outdoors by merging the two and designing spaces that flow from one to the other.

Calkins (2004) made several general recommendations based on the environmental press framework for improving both the physical and social environment of individuals with dementia. She stressed that in addition to the quantity of press in the environment, the quality, mobility, structure, predictability, and control over the press, among others factors, also must be examined. Calkins suggested that modifications can be made to the environment by 1) *reducing size* of space and number of individuals, thereby reducing the sources of stimulation; 2) *simplifying* visual and auditory stimuli, which can also apply to verbal commands made by care staff; 3) *providing options* by making areas of varying levels of press/stimulation available to residents; 4) *increasing familiarity* or meaningful stimuli in the environment, which also increases predictability; 5) providing *redundant cues* that may increase the likelihood of encoding by stimulating multiple senses; and 6) *emphasizing salient press* by increasing contrast between stimuli that should be attended to in the environment, as by placing a white dinner plate on a black table cloth.

General Assessment Issues Within the Social Environment

In terms of assessing person–environment fit, Calkins (2004) recommends learning about the individual's life before the onset of dementia. For example, knowledge of prior family size or individual characteristics such as introversion versus extraversion may give clues to the optimal amount of environmental press. Individuals who lived alone or with one other person most of their adult lives may be more vulnerable to overstimulation in long-term care units of moderate size than individuals who were frequently surrounded by many other people in their home environment. Cultural differences in the level of "boisterousness" or "reservedness" also may influence the amount of press individuals can handle (Calkins 2004). Moreover, knowledge of the family's shared history of memories before the onset of the disease may help patients maintain their identity (Cohen-Mansfield et al. 2000, 2006b).

Specific Assessments

Within the Community

Most individuals with dementia are cared for at home by family members (Burgio et al. 2008), but there are few guidelines for appropriate, reliable, and valid assessment of person–environment fit in community-dwelling persons with dementia (Gitlin 2003; Iwarsson 2005). Using the enabler concept that was developed as a basis for designing accessible housing and public environments (Steinfeld et al. 1979), Iwarsson and Slaug (2001) developed the housing enabler instrument to assess and analyze person–environment fit. Administration of the housing enabler instrument requires trained observers who are able to collect valid information on the personal component of the person–environment fit and to validate interview responses by means of observation of the home environment. It uses interview and observation to assess the functional limitations and dependence of the individual with dementia and includes observation of barriers. From these data, a person–environment fit score is calculated (Iwarsson 2005). For reliable score calculation, the housing enabler software is recommended (a demonstration version is available at http://www.enabler.nu).

Within Long-Term Care

As dementia progresses, a skilled nursing facility or other long-term care unit may be the most appropriate setting for care. Estimates of the prevalence of problem behaviors among patients with dementia in nursing homes range from 40% to 90% (Brodaty et al. 2001; Gruber-Baldini et al. 2004). Given the high prevalence rates, designing effective interventions for the management of behavior problems in long-term care has become a great health care concern.

An instrument that may be useful in the assessment of person–environment fit in long-term care settings is the Therapeutic Environment Screening Scale–2+ (Slaughter et al. 2006). Most items on this scale relate to the physical environment, but two of the three global ratings measure social interaction and engagement in activities. Of interest, a comparison using this instrument of special care facilities and with traditional institutional facilities focusing on environment quality found that dementia special care facilities were superior to traditional institutional facilities.

Interventions

The social environment within long-term care settings is comprised primarily of staff and other residents, although family and friends often continue to be involved. In this situation, residents' need for maintaining functional ability often conflicts with the staff's need to accomplish their tasks within a given period of time. These conflicts may have a detrimental impact on professional caregivers who are vulnerable to the effects of care-related burden as much as family caregivers (Allen et al. 2003a; Margallo-

Lana et al. 2001). Staff members' approach and response to the needs of persons with dementia is a large determinant of behavioral disturbance, making this an important point of intervention.

Issues Within the Social Environment

Across environmental settings, the characteristics of individuals with dementia, including sensory changes, cognitive and functional deficits, and behavioral and psychological symptoms, necessitate multicomponent interventions (Pinquart and Sorensen 2006). Although nonpharmacological interventions outnumber pharmacological interventions in the treatment of behavioral and psychological symptoms of dementia (Snowden et al. 2003), there are no firm guidelines for care. Behavioral interventions involve tracking antecedents and consequences of the behaviors of individuals with dementia, reinforcing desired behavior, and at times negatively reinforcing undesirable behaviors (Rusin and Lawson 2001).

Our discussion of intervention outcomes focuses on direct behavioral and environmental management of dementia patients. Chapter 20 of this volume, "Supporting Family Caregivers," describes interventions for family caregivers. A variety of other psychosocial interventions have been proposed for patients. Reality orientation has been reviewed by Spector et al. (2000), validation therapy by Deponte and Missan (2007), and reminiscence therapy by Scogin et al. (2005). Psychotherapy techniques have been reviewed by Finnema et al. (2000) and Baro (2002) and psychosocial interventions with more advanced dementia by Boote et al. (2006).

Tilly and Reed (2004), in a review of intervention research in nursing homes and assisted living facilities, categorized care for individuals with dementia in four areas. They are *physiological needs,* such as sleep, eating, toileting, and hydration; *hygiene-related needs,* such as bathing, grooming, and dressing; *ambulation and transfer-related needs;* and *behavioral and psychological aspects of dementia care* (e.g., disruptive vocalizations, aggressive behavior, suspiciousness). The first three areas generally are addressed through interventions in the physical environment, whereas interventions targeting behavioral and psychological aspects of dementia care often involve changes in the social environment of persons with dementia.

Physiological Needs

Meeting physiological care needs related to sleep, eating, and incontinence challenges formal and informal caregivers in community and long-term care settings. Family caregivers often struggle with the best ways to meet these needs and are eager to learn strategies to provide care in these areas. Modifications to the physical environment in the context of long-term care can minimize demands of staff and have a substantial impact on patient behavior.

Sleep

Disturbances in sleep are frequent in persons with dementia. Irregularities in circadian rhythms are thought to often be an underlying factor (Sloane et al. 2007). Numerous studies have examined the effect of bright light therapy or light exposure on sleep in persons with dementia (e.g., Mishima et al. 1994; van Someren et al. 1997). However, results appear to be mixed. It has been suggested that individuals with vascular dementia may be more likely to respond to light therapy than individuals with Alzheimer disease (Mishima et al. 1998). In one successful intervention utilizing light therapy, Sloane et al. (2007) observed sleep-wake cycles in 66 individuals with dementia using high-intensity ambient light in a crossover intervention trial in a psychiatric hospital and a dementia care facility. The most notable change was improved sleep for individuals with severe dementia exposed to a morning-light condition or an all-day light condition. Sleep may not be the only behavioral symptom that can benefit from bright light therapy; Mishima et al. (1994) found decreased agitation as well.

Eating or Feeding

Problems with poor food intake generally begin at the moderate stage of dementia and worsen with progression (Reed et al. 2005). Interventions have been designed to increase independent eating, caloric intake, and time spent at meals, but differences in outcome measures and low numbers of participants make a meaningful meta-analysis impossible at this time (Watson and Green 2006). Brush et al. (2002) improved oral intake and independent feeding by using high-contrast table settings, such as navy blue tray liners and white plates, and increased lighting in long-term care residences.

Van Ort and Phillips (1995) conducted a two-group (environmental and behavioral) study aimed at modifying antecedents of poor eating in a nursing home. They trained staff to minimize extraneous noise, to place residents at the dining table, to place food directly in front of residents or finger foods in the residents' hands. They sat functionally impaired individuals next to self-feeders, thus minimizing interruptions for staff engaged in feeding residents. Staff used verbal and tactile prompts, repeated instructions, modeled desired behaviors, and reinforced self-feeding attempts. Both environmental and behavioral

interventions increased independent self-feeding among residents. The investigators concluded that the behavioral intervention also promoted longer resident–staff interactions and seemed to provide a better person–environment fit for the functional abilities of the residents.

Incontinence

Despite the high prevalence of incontinence in persons with dementia, behavioral and environmental modifications to treat incontinence are underutilized in the community and within long-term care settings. Incontinence can lead to social withdrawal, depression, and discomfort and directly effects emotional well-being and quality of life (Burgio et al. 1998). Placing a picture of a toilet on the door to public restrooms in institutional settings or removing the door from private restrooms within apartments or residents' rooms can also increase toilet visibility and independent toilet use (Calkins 2001). The best behavioral approach is training caregivers to take dementia patients to the toilet every few hours and to be certain that their patients urinate before leaving home or the long-term care facility. Education of caregivers about the causes of incontinence is also warranted, because some may attribute fecal or urinary incontinence to laziness or malevolence rather than progression of dementia.

Environmental design should also be considered when planning new facilities. For example, Noreika et al. (2002) made recommendations for designing bathrooms that promote use by residents and facilitate care tasks of care providers or staff by including elements that promote comfort, ensure safety, and are easy to access and clean.

Pain

There is often reluctance to use patient self-report in the assessment of person–environment fit, but recent research suggests that individuals with Alzheimer disease with Mini-Mental State Examination scores as low as 15 can give reliable self-report data relevant to pain (Fisher et al. 2006) and quality of life (Logsdon et al. 2002). Simmons and Schnelle (2001) provided an empirically supported and objective method for identifying nursing home residents capable of accurate self-report of quality of care. They suggest that nursing home residents who can on two separate trials state their name on request or reliably identify two objects (i.e., watch and pencil) are capable of reliable self-reporting of quality of care.

Hygiene-Related Needs

Needs related to hygiene place high demands on informal caregivers and nursing home staff (Sloane et al. 2004). Acts of physical and verbal aggression occur most often during daily care routines, further complicating the provision of care to individuals with dementia (Baker et al. 2006). From an environmental-press perspective, bathing, dressing, and oral care may overstimulate and cause discomfort for many patients with dementia. If resistance, in the form of physical or verbal aggression, is rewarded by "escape" or avoidance of the excessive environmental press (e.g., daily care), then differential reinforcement of other behaviors (i.e., providing positive reinforcement contingent on nonagitated behavior) during care or extinction may be appropriate (Baker et al. 2006). Modifying the amount of environmental press or stimulation experienced by each patient by adjusting both physical and social interaction during care routines can make these routines a more pleasant experience for care providers and patients.

Promoting Independent Care

An objective of environmental-press models and many community and nursing home interventions is to slow the rate of dependence in activities of daily living. For example, in a study targeting oral care, individualized environmental modifications were designed to increase good oral hygiene in nursing home residents (Connell et al. 2002). Successful modifications included visual cues such as a picture of a mouth used in combination with verbal prompts, introduction of toothbrushes with extra long handles and textured grips, colorful disposable cups for mouthwash and rinsing, and a consistent layout of oral care products. Rolland et al. (2007) were able to slow dependence in activities of daily living by introducing a biweekly, 1-hour exercise program.

Dressing

Dressing is a complex behavior that has rarely been studied closely. Analysis of videotaped dressing routines of residents in a dementia-specific unit revealed that daily care routines were an underutilized opportunity for social interaction and physical stimulation or touch (Cohen-Mansfield et al. 2006a). Both communication and presentation of choices was minimal. The mandated wearing of gloves during care has the unfortunate consequence of reducing comforting direct touch, which has been linked with increased well-being in individuals with dementia by Woods et al. (2005). Other research has suggested that even simple interventions such as presenting clothes sequentially (undergarments first, etc.) can improve independence (Day et al. 2000). Namazi and Johnson (1992) designed an interactive closet for institutional settings that provided clothes for residents in set order.

Bathing

Bathing can be personal and enjoyable or dehumanizing and embarrassing for the individual with dementia. Person-centered bathing and towel baths have been shown to reduce disruptive behaviors and agitation during bathing (Whall et al. 1997), but many person-centered approaches may not be realistic in everyday care settings as they frequently do not consider the needs of the care provider. To deal with this, Cohen-Mansfield and Parpura-Gill (2007) designed an intervention that addressed the needs of the individual with dementia, the care provider, the physical environment, and the institution that decreased agitated behaviors and increased positive affect and positive staff reports; the details are reported in their publication.

Martin et al. (2004) implemented an educational intervention focused on improving care providers' knowledge and techniques regarding bathing individuals with dementia. Using the acronym ART (acknowledge, respectfulness, tenderness), 45 care providers were trained in bathing strategies specific to individuals with dementia. Although patient outcomes were not obtained, caregivers had enhanced knowledge in areas of communication (use of short verbal commands, inviting the patient to participate in care, socially engaging the patient in an area of interest), towel bathing techniques (approaching bathing as a pleasurable experience for the patient, allowing the patient to remain warm and covered throughout the bathing procedure, using gentle massage, and use of small disposable towels for different areas of the body), and problem solving related to bathing care. Martin and colleagues had each care provider practice newly learned skills on one of their patients and write case studies of their experience as part of the intervention. Mickus et al. (2002) implemented a similar educational intervention using the acronym PRIDE (privacy, reassurance, information, distraction, and evaluation), which reduced problem behaviors and resident anxiety and irritability related to bathing.

Ambulation and Transfer-Related Needs

Ambulation and transfer-related needs encompass a broad array of care spanning from driving-related interventions to issues related to transfer and more basic ambulation.

Driving

Cognitive changes that occur as a result of normal aging can affect drivers' ability to successfully operate a car, particularly in demanding driving conditions (Anstey et al. 2005). Drivers with even mild dementia are at increased risk of accidents, becoming lost, ignoring road signs and traffic patterns, and other adverse events. Like many other areas of dementia care, there is no set of guidelines to facilitate driving cessation of individuals with dementia, and prohibiting driving can be seen as a threat to autonomy. The Hartford Foundation (2007) has published a document describing signs that may indicate the need for additional assessment or caution. Among the signs were riding the brake, hitting curbs, near misses, confusion at exits, reliance on a copilot, and failure to notice traffic signals. In addition to offering a checklist of behaviors to monitor, this organization also offers helpful hints for discussing this with loved ones and advice for dealing with a resistant individual.

Mobility

Trouble with transfer, ambulation, and mobility in dementia may hinder social activity in nursing homes. In a stratified sample, Dobbs et al. (2005) observed decreased activity in 400 elderly individuals (mean age=85 years) in long-term care settings using the Patient Activity Scale–Alzheimer's Disease (Albert et al. 1996). They found lower activity levels among individuals in nursing homes than individuals in assisted-living facilities despite similar levels of cognitive decline and number of activities offered. They also found that family involvement was related to activity level, suggesting a need for increased involvement of families for many persons.

Mathews et al. (2000) introduced rhythmic music during exercise sessions to increase exercise participation in a dementia care facility. The intervention had a positive effect on exercise participation, a means to increase mobility and social engagement. Effective fall prevention can also promote increases in engagement and can be achieved through interventions such as the introduction of low chairs, railings, and nonskid mats (Day et al. 2000; Rask et al. 2007).

Behavioral and Psychological Symptoms of Dementia

Rusin and Lawson (2001) describe various barriers to the implementation of behavioral interventions for persons with dementia by family caregivers (e.g., caregiver priorities, caregiver fatigue, role changes) and suggest specific approaches to increase family caregiver use of behavioral interventions. They make recommendations for addressing depression, aggressive behaviors, sexually inappropriate behaviors, and behaviors that frighten or irritate caregivers. Differential reinforcement of other behavior, time out, restriction, or stimulus control (changing the properties of the stimuli that trigger a behavior) has also been implemented to positive effect with persons with dementia.

Depression and Anxiety

As noted in Chapter 15 of this volume, depression and anxiety are common in persons with dementia. Logsdon et al. (2005) have developed a behavioral intervention, the Staff Training in Assisted Living Residences—Caregivers (STAR-C) program, to decrease depression and anxiety in individuals with Alzheimer disease. Based on social learning theory and principles of behavior analysis, STAR-C teaches caregivers to view withdrawn behaviors and agitated patient behaviors as modifiable. STAR-C teaches caregivers to interact with their loved ones by providing pleasant events that reinforce positive affect and prevent or minimize depressive or anxious behaviors. The program consists of eight weekly in-home sessions followed by four monthly telephone calls and is implemented by community-based mental health practitioners. These practitioners taught caregivers basic information about Alzheimer disease, the principles of behavior change, the ABC model of behavior, communication skills, and how to engage the individual with dementia in pleasant events. STAR-C assisted caregivers, and individuals with dementia had fewer altercations and more engagement in pleasant events. Additionally, the program increased continence, reduced resistance to bathing and physical care, increased activity, and reduced behavior problems.

Meeks and Depp (2002) described a promising behavioral intervention for the treatment of depression based on earlier work (Teri 1994; Teri and Logsdon 1991), incorporating increased pleasant events into the daily lives of individuals with dementia. They hypothesized that depression in individuals with dementia is partly a result of inability to generate independently positive reinforcers in the social and physical environment. Nursing staff and available family members were trained to build pleasant events such as videos, music, interaction with pets, and conversation into patients' daily schedule, to observe the most reinforcing events, and to increase their frequency over time. Meeks and Depp underscored the importance of care providers understanding the relationship between pleasant events and positive emotional state as a means to maintain intervention efforts over time.

Agitation

Kovach (2000) developed a theoretical model for explaining agitation in individuals with dementia built on principles similar to those proposed by Lawton (1986). She argued that an imbalance in "sensoristasis," an inequity in sensory-calming and sensory-arousing stimuli, is at the root of agitated behaviors. Based on this model, Kovach et al. (2004) designed the Balancing Arousal Controls Excess intervention to reduce agitation for individuals in long-term care with moderate to severe dementia. The intervention was designed to break up periods of unengaged time with sensory stimulation and break up periods of time characterized by persistent stimulation with periods of low-arousal activities. This intervention achieved significant results (P=0.043) in a randomized, double-blind study of 78 persons in long-term care.

Another intervention attempting to reduce agitation and distress through physical stimulation did not meet the same success. In an uncontrolled study, Snyder et al. (2001) introduced a daily 20-minute glider swing intervention for a period of 10 days in 30 individuals with dementia in long-term care facilities. This brief intervention did not have a significant impact on aggression. On the other hand, staff motivational systems have been shown to decrease agitation and to maintain the decrease over 6 months (Burgio et al. 2002).

One type of agitation is disruptive vocalizations, including loud requests for attention, chronic screaming, moaning, self-talk, negative remarks, and use of obscenities (McMinn and Draper 2005). Disruptive vocalizations are one of the most common forms of behavioral disturbance found in nursing homes, occurring in up to 30% of residents (Cariaga al. 1991; Sloane et al. 1999). Even though numerous intervention strategies have been used to decrease the frequency of disruptive vocalizations and thus improve the living and working conditions of the nursing home for residents and staff, there is no consensus on the best way to treat these behaviors. Based on a review of the literature, McMinn and Draper (2005) suggested that interventions be tailored to the individual case and etiology, that multiple, simultaneous interventions may be necessary, and that a residual level of disruptive vocalizations remain in most cases. Their general recommendations included reducing meaningless environmental stimuli, placing an emphasis on nonverbal communication, relieving immediate discomforts, and providing orientation cues.

Another manifestation of agitation is aggression. Physically aggressive behaviors include pushing, spitting, grabbing, kicking, hitting, and dangerous, assaultive behaviors (Burgio and Stevens 1999; Cohen-Mansfield et al. (1989a, 1989b) and are associated with negative staff outcomes such as job stress, burnout, and turnover (Burgio et al. 2004). Common antecedents to aggressive behavior include anticipation of pain, as in the changing of wound dressings, and frustration with one's inability to perform daily care tasks independently (Baker et al. 2006; Cohen-Mansfield et al. 1990). Impaired communication and depression also lead to aggression within the nursing home (Talerico et al. 2002). Therefore, interventions designed to address depression and other underlying factors may also

decrease levels of aggression. Finally, educational interventions for staff can be helpful in identifying antecedents or other behavioral cues that may precede aggressive acts by residents (Chrzescijanski et al. 2007), which aids in modifying social triggers within the individual's environment. Functional analysis of nursing home resident behavior revealed that increased aggression during daily care routines such as bathing was maintained through reinforcing avoidance. Noncontingent reinforcement of escape was implemented, and aggression was nearly eliminated (Baker et al. 2006).

Wandering

Wandering is a frequent, potentially dangerous dementia-related behavior (Yao and Algase 2006). The mortality rate for missing individuals with dementia is 40% after 24 hours (Koester and Stooksbury 1995). It has been estimated that in a given week in the United States at least one individual with dementia will wander off the premises of a nursing facility and die (Kennedy 1993). Therefore, it is not surprising that physical restraint use increases in individuals who are inclined to wander (Burton et al. 1992). Within community care settings, safe pathways throughout the home can be highlighted through the use of nightlights for persons who wander. Unfortunately, there have been no randomized trials of nonpharmacological interventions for wandering in domestic settings (Hermans et al. 2007).

Appropriate environmental designs within a long-term care setting can provide a safe environment for self-soothing wandering behaviors. Individuals with the greatest cognitive impairment are the most likely to wander (Yao and Algase 2006), making it a problem of great concern to nursing home staff (Lai and Arthur 2003). Interventions include outdoor walks (Cohen-Mansfield and Werner 1999) and use of wandering areas (Namazi and Johnson 1992) or enhancing environments to facilitate group interaction or rest.

Differential reinforcement through alteration of social and physical contingencies also can be used to alter wandering behaviors in long-term care settings. Heard and Watson (1999) observed wandering behaviors in residents and identified reinforcers for wandering as a first step to introducing a behavioral modification plan for individual patients. Then they applied the same reinforcers (i.e., attention, tangible items, and pleasant sensory consequences) in the absence of wandering behavior, which decreased the undesirable behavior by up to 75%.

Coping patterns, previous work roles, and tendencies toward greater affiliation (i.e., seeking familiar places and people to provide security) are also associated with wandering behaviors (Goldsmith et al. 1995). Addressing these areas is essential. Yao and Algase (2006) emphasized the impact of "environmental ambiance" on wandering behaviors. The model of Locomoting Responses to Environment in Elders With Dementia (Yao 2004) is based on the assumption that emotional information in the environment is processed differently than cognitive information. Furthermore, Yao argues that the affective triggers in the environment are experienced by individuals with dementia even after other perceptual discriminations are lost. Thus, individuals with severe levels of dementia may only perceive the basic, automatic affective impressions, or press, of "avoidance" or "approach" from a given stimuli or environment. Yao and Algase (2006) studied 47 residents with probable dementia in nursing homes and assisted living facilities to assess the effects of environmental ambiance on wandering behavior. They found that engaging environments that evoked positive emotions promoted "staying" behavior, whereas environments that did not engage evoked avoidance behavior and increased wandering. It is also likely that some episodes of wandering are related to understimulation. Enhanced environmental designs (Calkins 2004; Chalfont and Rodiek 2005; Ruckdeschel and van Haitsma 2001), which introduce components into the environment such as plants and other soothing, engaging stimuli such as pets, might decrease wandering.

Social Interaction/Communication

A number of methods have been suggested to promote social interaction, including use of videotapes of family members talking to their relative with dementia (Cohen-Mansfield and Werner 1997; Werner et al. 2000) and simulated presence (Camberg et al. 1999; Woods and Ashley 1995), in which a family member audiotapes one side of a phone conversation. There are also commercially available videos incorporating familiar music sing-alongs. Pet therapy (Churchill et al. 1999; Libin and Cohen-Mansfield 2004) also provides interaction with animals and conversation topics for cognitively compromised individuals.

Dolls have also been used to simulate presence for nonverbal individuals with dementia. Dolls are particularly well suited for socially withdrawn residents experiencing distress or communication difficulty in nursing homes. Dolls may serve both a social and tactile stimulation role and reduce agitation and distress, although at times they are seen as demeaning by family or staff (James et al. 2006). Clinicians currently are working to develop manualized treatments for use of dolls in nursing home settings, which would facilitate a more systematic approach to this simple, cost-effective intervention (Mackenzie et al. 2006).

Staff training and staff motivational systems in nursing homes have also been shown effective in improving staff-resident interaction. Burgio et al. (2001) found that

training-certified nursing assistants in communication skills and providing residents with memory books covering meaningful aspects of their past lives succeeded in improving positive communication between residents and nursing home staff. This intervention also seemed to improve resident-to-resident communication (Allen-Burge et al. 2001).

Interdisciplinary Care and Translational Research

Our review of intervention research, characteristics of persons with dementia and their environment, and theoretical models of person–environment fit point out the interdisciplinary nature of care for individuals with dementia (Calkins 2004; Keough and Huebner 2000). Specific models of interdisciplinary care have been proposed, including the Project for the Regional Care of Patients Suffering From Dementia and Their Care-Providing Relatives (PRO DEM) project (Hesse 2005), that incorporate physicians, nurses, and speech therapists into treatment planning. Moreover, Keough and Huebner (2000) propose integrating occupational therapy and psychology to facilitate optimal care in community and long-term care settings. They propose that occupational therapy take the lead in producing recommendations for modifying the physical environment, maximizing residual strengths of the individual with dementia, and defining small potential changes with large behavioral impact. In their model, psychologists would take the lead in facilitating interdisciplinary team development and maintenance and incorporating caregiver interventions to improve the well-being of individuals with dementia. In contrast, Calkins (2004) and others highlight redesign of the physical environment, necessitating input from engineers, builders, and behavioral and social scientists. Cohen-Mansfield (2003) provides the most integrated model of optimal interdisciplinary care, including recommendations for how conflict of interest between stakeholders might be resolved. Such interdisciplinary care models are informative in the design of translational research, the ultimate goal of which is to transfer our research knowledge of environmental and behavioral interventions into the community and long-term care settings, in which staff can use the interventions in their everyday practice.

Three ongoing areas of research in different stages of translation include stimulating role identity of the person with dementia (Cohen-Mansfield et al. 2000, 2006b), train-the-trainer programs in which community stakeholders such as personnel from an Area Agency on Aging are trained to assess the needs of families they serve and to implement interventions, and use of staff motivational systems incorporating skills training in behavior management techniques to ensure the continued implementation of interventions in long-term care facilities.

Cohen-Mansfield's Work With Role Identity: Early Stages of Translation

Cohen-Mansfield et al. (2000) have explored means to maintain the self-identity or personhood of individuals with dementia. They used semistructured interviews and close-ended questionnaires (Self-Identity in Dementia Questionnaire) with elderly persons with dementia, their formal caregivers, family members, and, when appropriate, review of the medical chart. These interviews targeted four general roles or domains of identity: family membership, work, leisure activities, and identity related to group membership, trait, or achievement. Cohen-Mansfield and colleagues found that individuals with dementia reported the following salient identity roles, in order of prevalence: 1) family heritage, 2) success of a relative, 3) academic achievement, 4) occupations, 5) traits, and 6) survival.

Later, Cohen-Mansfield et al. (2006b) implemented interventions designed by research staff but involving family member and long-term care staff interactions with the individual with dementia. Each intervention was designed to target relevant aspects of individuals' self-identity and involve family members and staff in reinforcing and maintaining these roles. In 93 older persons with moderate to severe dementia, there was a significant increase in interest, pleasure, and involvement with activities, fewer agitated behaviors, and increased orientation during the treatment period. The interventions in this project were designed by research staff and implemented by family caregivers and professional staff. Thus, this project exemplifies translational research in the earliest stages. Future studies should explore the feasibility of having family caregivers and professional staff members design the interventions to be used with patients.

Train-the-Trainer Interventions in Community Settings

Two further examples of translational interventions have been conducted by Sabata et al. (2005) and Burgio et al. (in press). Sabata et al. developed Project CARES (Caregiver Adaptations to Reduce Environmental Stress) and implemented it through the National Family Caregiver Support Program. Project CARES, a 2-year demonstration project,

developed online training for Area Agency on Aging (AAA) staff to educate caregivers about environmental interventions such as assistive devices and home modifications to improve the functioning of individuals with dementia. The first year of the project focused on needs assessment for each family served by AAA staff participants and development of an online training module that incorporated a Web manager available by phone and e-mail to answer technology-related questions. The second phase of the project involved 40 AAA staff members who attended two training sessions and were asked to apply this training in their local community agencies.

The CARES intervention lasted for 10 weeks and consisted of four online sessions with weekly exercises, a teleconference at week 5, four more online lessons, and a final proposal assignment completed by AAA staff due in week 10. Among other topics, the online lessons included information regarding 1) home modifications and assistive devices, 2) identification of major caregiving activities that cause physical burden and their relationship to the environment, 3) identifying environmental solutions and caregivers' educational needs, 4) community and family resource identification, and 5) developing a specific plan of action. Fifty percent of AAA participants from 18 states completed training. The project worked best in AAAs that received the most local support, agencies with some services already in place or a basis of knowledge for expanding possible home modification services, and agencies that set achievable goals that could be realistically implemented within 6 months.

Similar to the CARES project, Burgio et al. designed a demonstration project to translate the success of the two Resources for Enhancing Alzheimer's Caregiver Health (REACH) trials for implementation by AAA staff within the community. The Alabama Department of Senior Services (ADSS) partnered with The University of Alabama to develop the demonstration project. Through an advisory committee consisting of the university principal investigator and project manager, the executive director of ADSS, and the AAA case managers and supervisors, the REACH II intervention (Belle et al. 2006) was modified for use within the AAAs. The interventionist and caregiver manuals were shortened and simplified, treatment sessions were reduced from twelve over 6 months to four home sessions over 4 months, and treatment components were reduced to five: 1) education about Alzheimer disease and caregiving, 2) caregiver health, 3) home safety, 4) behavior management, and 5) stress management. All aspects of the program were controlled by the AAAs, with consultation from university personnel.

Analyses of 236 dyads suggested positive pre and post changes in overall burden, social support, depression, positive aspects of caregiving, potentially harmful behaviors, and risky behaviors, such as leaving the persons with dementia unsupervised. The intervention, every component in the intervention, and the procedures were reported by family caregivers and AAA staff to be highly acceptable. However, in a focus group follow-up, AAA staff reported the need for more information on bereavement and communication with health care professionals.

Staff Motivational Systems in Long-Term Care

Burgio and Stevens (1999), Burgio et al. (2001, 2002), and Stevens et al. (1998) have presented a detailed staff motivational system for use in long-term care settings to facilitate the implementation of environmental and behavioral interventions with residents by nursing staff. Didactic and active skills training on the job are included. Didactic training covers five major skill areas: 1) identifying environmental antecedents to resident problem behaviors, 2) identifying the ABCs of residents' behaviors, 3) communication skills training, 4) training in positive reinforcement procedures, and 5) training in distraction and diversion techniques. Intensive on-the-job training involves research staff and nursing staff working together to design individualized behavior programs targeting specific behavioral and psychological symptoms of dementia displayed by each resident. Most importantly, supervisory nursing staff and certified nursing assistants receive behavioral observation and feedback from research staff and from their in-house supervisors regarding their use of behavioral skills. Certified nursing assistants are enrolled in a performance-based lottery to reinforce accuracy in treatment delivery in providing care to individuals with dementia.

This 17-year program of research found that long-term care staff can successfully be trained to implement and maintain environmental and behavioral interventions. Specifically, nursing staff used memory books and communication skills to increase positive interactions between staff and residents (Burgio et al. 2001, 2002) and between residents (Allen-Burge et al. 2001). Communication skills were also improved, as reflected by increased use of one-step instructions (Burgio et al. 2001). Although initial training gains were observed on all units receiving didactic and skills training, only units implementing the staff motivational system for maintenance of the intervention within the facility actually maintained intervention gains over time (Burgio et al. 2002).

Conclusion

Intervention research targeting person–environment fit based on Lawton and Namehow's Competence Press Model has increased exponentially and improved methodologically in the past several years. Areas of current scientific and clinical interest include 1) the integration of life span development theories similar to Baltes and Baltes's (1990) selective optimization with compensation metatheory into investigations of motivation among individuals with dementia (Wahl and Lang 2004), 2) increased interest in the emotional experience and well-being of the person with dementia, including assessment of positive affect and the maintenance of identity, and 3) efforts to create and promote culture change within community and long-term care settings that prioritize person-centered programs, person–environment fit, and dementia-capable care (Keane and Shoesmith 2005).

We believe that methodological innovations in the assessment of person–environment fit may facilitate the development of interventions that will enhance the positive affective experience of the individual with dementia. To date, however, evidence supporting associations between positive affect and environmental competence has not been strong. In a study of 134 residents from 22 different facilities, neither facility size nor homelike environment predicted quality of life (Samus et al. 2005). Thus, creating cozy, smaller, homelike environments may not be enough to promote quality of life in patients with dementia without improving the social environment through training family caregivers and professional direct care staff.

Integrating assessments of person–environment fit into real-world settings will require the integration of multiple partners in care. Few interventions can be directly transferred from a research protocol to everyday applications. Feasible versions of person–environment fit assessments must be created for real-world implementation. Once brief and reliable needs assessments can be conducted by direct care providers, effectiveness studies can be implemented to examine evidence-based treatments as conducted in the real world. This requires commitment on the part of the multiple partners in care to the well-being of the individual with dementia. It also requires culture change supportive of new and interdisciplinary approaches to care and, potentially, greater autonomy on the part of direct care staff with skills training needs.

KEY POINTS

- Lawton and Namehow's Competence Press Model is a helpful tool for conceptualizing the interaction between an individual with dementia and his or her environment.
- Environmental and behavioral interventions must be designed to maximize person–environment fit within the competence of each individual.
- Innovations in the assessment of person–environment fit may promote attention to the affective experience of the individual with dementia and his or her self-identity.
- Active treatment components of current evidence-based interventions must be identified for real-world implementation.
- Culture change in care systems requires changes in policy at the local, state, and federal levels.

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CHAPTER 18

Pharmacological Treatment of Alzheimer Disease and Mild Cognitive Impairment

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In this chapter we review the drugs currently approved in the United States for treatment of cognitive symptoms of dementing disorders. None has yet been approved for mild cognitive impairment (MCI), but many physicians treat these individuals with the medications that are available for Alzheimer disease. We focus primarily on drugs for which there are double-blind, placebo-controlled studies, but a few widely used drugs are considered for which there is less vigorous evidence for efficacy. It has been recognized that drugs aimed primarily at improving cognitive deficits may also have an impact on behavioral and psychiatric symptoms (Cummings 2000). In this chapter we present the effects of drugs used to treat cognitive symptoms in Alzheimer disease on both cognitive and behavioral symptoms. (The latter also are mentioned in Chapter 15 of this volume, "Psychiatric Disorders in People With Dementia.")

General Principles

The rational use of drugs for treating cognitive deficits is aided by an accurate diagnosis of the cause of patients' symptoms, by knowledge of patients' past medical history including prescription and nonprescription drug use, and

by a complete physical and neurological examination to detect potentially reversible causes of cognitive impairment such as urinary tract infection or hypothyroidism. Other comorbid illnesses also must be considered for their potential to be negatively affected by the medications commonly prescribed for dementia (e.g., ulcer disease, obstructive pulmonary disease, arrhythmias). Medical, social, and psychological histories are also important because they may indicate one or more factors precipitating the presenting symptoms, such as a change of environment, as indicated in the following example:

Case 1

The daughter-in-law of Mrs. J, an elderly woman with Alzheimer disease enrolled in a cognitive-enhancer study, called and expressed alarm that Mrs. J initially had a good response to the drug under study but had suddenly worsened. When asked to describe what had happened, she told the physician that Mrs. J had been living with her and her husband for about 1 month. They had gone to the apartment where Mrs. J had formerly resided to pack up more of her possessions. While there, Mrs. J suddenly became very confused and no longer recognized her son. They took her back to their home, where she sat on her bed crying out for her own mother. The physician reassured the daughter-in-law that Mrs. J had experienced a catastrophic response to the emotional stimulus of giving up her apartment and her former lifestyle and that with a day or two to adjust, her symptoms would probably improve. The daughter-in-law called the next morning to say that indeed all was well again.

Many medical conditions have the potential to worsen cognition in dementing illnesses. This is especially important in late-stage dementia patients who are unable to report their physical symptoms resulting from urinary tract infection, arthritis, vertebral compression fractures, etc. Having ruled out or treated medical conditions that may precipitate or worsen cognitive symptoms, the physician should also review the patient's medications for drugs that may produce confusion or alter mood. In some cases, eliminating the medication or reducing the dosage of one of these drugs may be more effective than adding a cognitive enhancer.

Certain classes of drugs should be avoided or used in the minimum dosage needed to treat the illness underlying the patient's symptoms. For example, the cholinergic deficit characteristically seen in Alzheimer disease makes these individuals highly susceptible to further impairment of sensorium by anticholinergic drugs or drugs with anticholinergic side effects. Thus, the use for sedation of antihistamines such as diphenhydramine (Benadryl) is relatively contraindicated, as are strongly anticholinergic antidepressant medications such as amitriptyline (Elavil). The bladder relaxants oxybutynin (Ditropan) and tolterodine (Detrol), although primarily having peripheral cholinergic effects, also can act centrally and should be used with caution (Katz et al. 1998; Womack and Heilman 2003). Physicians caring for late-stage dementia patients often must weigh the potential deleterious effects of these medications on cognition versus their beneficial effects in treating urinary incontinence, a symptom that family caregivers often have difficulty managing in a home environment. Arginine vasopressin can sometimes be substituted for the anticholinergics for nighttime urinary incontinence without adverse cognitive effects. The following sections cover drugs or other substances that are in wide current use in the United States. Some are approved by the U.S. Food and Drug Administration (FDA) for use in Alzheimer disease; others are not. Promising and experimental drugs or substances are discussed in Chapter 25 of this volume, "The Future of Dementia Treatment."

Cholinergic Augmentation

Precursors of acetylcholine, cholinomimetics, and anticholinesterases have been used to treat Alzheimer disease. Their use is based on the observation that cholinergic neurons are selectively reduced in Alzheimer disease (Davies and Maloney 1976) and on the deleterious effects of anticholinergic and cholinomimetic drugs on memory. For example, Drachman and Leavitt (1974) showed that scopolamine impaired the storage of information in long-term memory with relative sparing of recall and retrieval from long-term memory—a finding resembling impairments known to occur with normal aging. The effect of scopolamine on memory is reversed by physostigmine (Granacher and Baldessarini 1976). Furthermore, physostigmine has direct memory-enhancing effects when carefully titrated in humans (Davis et al. 1987). Based on these findings, three main approaches have been investigated to increase cholinergic transmission: increasing substrate available for the biosynthesis of acetylcholine, using cholinomimetics to augment acetylcholine activity, and blocking the degradation of acetylcholine to prolong its activity at receptor sites. However, Davis et al. (1999) showed that activity of the cholinergic marker enzymes choline acetyltransferase and acetylcholinesterase in nine cortical regions in subjects with Alzheimer disease did not differ significantly from control subjects until the affected persons had clinically severe disease as indicated by premortem Clinical Dementia Rating Scale (CDR) (Hughes et al. 1982) scores of 3 to 5. Thus, they suggested that cholinesterase inhibitors may be more effective in more advanced disease, a suggestion that is not borne out by clinical experience.

TABLE 18–1. Dosages of anticholinesterases

Generic name	Trade name	Initial dosage (mg/day)	Optimal individual dosage (mg)	Frequency of dosage
Tacrine	Cognex	40	40	qid
Donepezil	Aricept	5	10	qam
Rivastigmine	Exelon	3	6	bid with food
	Exelon patch	4.6	9.5	qam
Galantamine	Razadyne	8	8–12	bid
	Razadyne ER	8	24	qam with food

Note. Dosages should be increased no sooner than 4 weeks. qam=every morning; qd=every day; qid=four times a day; bid=twice a day.

Precursors

Acetylcholine is produced in the brain by the acetylation of choline through the action of the enzyme choline acetyltransferase and the cofactor coenzyme A. Initially used in supplementation trials, lecithin (whose primary constituent is phosphatidylcholine) was ineffective, made patients malodorous, and also did not improve cognitive function. It has been more recently found that active transport mechanisms make it difficult to greatly raise levels of these precursors in the brain. There is little evidence that either lecithin or phosphatidylcholine is useful in ameliorating the cognitive deficits in Alzheimer disease.

Similarly, acetyl-L-carnitine, marketed in Italy as Nicetile for treatment of cognitive impairment, is available in the United States as a food supplement. It is a naturally occurring substance that may help in the formation of acetyl coenzyme A or acetylcholine. It has been used in Alzheimer disease and vascular dementia. In a 1-year placebo-controlled study in persons with mild to moderate probable Alzheimer disease, the drug did not differ from placebo in a dosage of 3 g/day (Thal et al. 1996). In a subanalysis, patients with early-onset disease appeared to show greater improvement that those with late onset. A subsequent study of the substance in early-onset cases was abandoned because of recruitment difficulties.

Cholinomimetics

Carbachol, a direct muscarinic receptor agonist, was tried as a treatment for Alzheimer disease but caused substantial nausea and vomiting. It was thought that other drugs such as milameline and xanomeline, which are more selective for muscarinic receptor subtypes, would be less likely to cause side effects. Trials of these agents showed modest benefits in cognition and behavior, but patients had frequent sweating, nausea, vomiting, diarrhea, and syncope. The cholinomimetic approach to Alzheimer disease has been largely abandoned because of drug toxicity, including induction of depression by the cholinergic agonist oxotremorine (Davis et al. 1987).

Anticholinesterases

The anticholinesterases (Table 18–1) have been the most successful cognitive enhancers for Alzheimer disease. Of these, tacrine (Cognex) was introduced in 1993, donepezil (Aricept) in 1997, rivastigmine (Exelon) in 2000, and galantamine (Reminyl/Razadyne) in 2001. All four drugs are reversible inhibitors of acetylcholinesterase. Rivastigmine also reversibly inhibits butyrylcholinesterase; galantamine has additional effects in regulating nicotinic receptors. The therapeutic and side effects of all these drugs are very similar except for the hepatotoxicity caused by tacrine. Although the cholinergic system appears to be involved integrally in the encoding of memory, the effects of anticholinesterases in Alzheimer disease appear to be more general, augmenting executive functioning as well as memory, and are likely to alter positively the complex interactions between cholinergic, noradrenergic, and dopaminergic systems (Robbins and Roberts 2007). This is supported by an observational cohort study comparing 65 persons treated for Alzheimer disease with cholinesterase inhibitors matched with an equal number of untreated persons, which found less decline over 1 year in the treated group in functioning in activities of daily living, overall cognition, and all subscores of the Dementia Rating Scale (Mattis 2005) except memory.

Tacrine

An aminoacridine derivative marketed as Cognex in 1993 was the first evidence-based regulatory authority–approved treatment for Alzheimer disease in the United States. In the 30-week, double-blind, placebo-controlled

pivotal trial supporting approval, only 40% of treated patients in the 160 mg/day target dosage group achieved a clinically significant improvement, and only 27% of these subjects were able to achieve and remain on that dosage through the end of the study. Therefore, it was calculated that only 12% of patients who were initially starting treatment achieved clinically significant symptomatic improvement. Tacrine also required four-times-a-day dosing and titration from 40 mg/day to 160 mg/day to reach the most effective dosage, as well as periodic monitoring of liver functions, particularly during the initial titration phase of treatment. It has been reported that patients who continued taking dosages of tacrine of 80 mg/day or more for 2 years were less likely to be admitted to nursing facilities than those taking lower dosages (odds ratio, 2.7 for >80 mg/day; 2.8 for >120 mg/day) (Knopman et al. 1996). This finding is difficult to interpret because of the bias introduced by attrition (Knopman et al. 1998). Because of its tolerability issues, frequency of dosing, and the need for close monitoring, use of tacrine largely has been abandoned.

Donepezil

This piperidine-based reversible acetylcholinesterase inhibitor, marketed as Aricept since 1997, reaches peak plasma concentrations 2–4 hours after an oral dose. It is 100% bioavailable, and food has no effect on its absorption. The drug is more than 90% protein bound. Plasma concentrations increase linearly with dosage increase. The half-life of the drug is approximately 70 hours. At 5 mg/day, donepezil produces 64% red blood cell cholinesterase inhibition (Crismon 1998). A relationship has been shown between the cognitive effect of donepezil and the degree of plasma acetylcholinesterase inhibition, but a plateau of acetylcholinesterase inhibition was reached at plasma concentrations greater than 50 ng/mL (Rogers and Friedhoff 1996). However, recent studies have suggested levels of cholinesterase inhibition in brain may lag and be considerably less than in red cells or plasma. In the initial pivotal 24-week, double-blind, placebo-controlled study, roughly 80% of patients receiving 5 mg or 10 mg of donepezil showed no cognitive worsening at at least one follow-up time point on the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen et al. 1984) compared with 42% of the placebo group (Rogers et al. 1998). On a measure of global function, approximately 25% of the donepezil-treated group (5 or 10 mg) improved compared with 11% of the placebo group. Thus, the overall effect of the drug was to maintain patients at their baseline level on symptomatic functioning for approximately 24 weeks, whereas those receiving placebo declined below baseline.

A large double-blind, placebo-controlled, 48-week, randomized donepezil study removed patients from the blinded portion of the study if they deteriorated in their activities of daily living (ADLs). By the end of the study, 51% of patients with Alzheimer disease had not progressed in their ADLs versus 36% in the placebo group (Mohs et al. 2001). The so-called Nordic study also treated mild to moderate Alzheimer disease for 1 year with best dose of 5 mg or 10 mg compared with placebo in a randomized double-blind trial (Winblad et al. 2006b). In this study, donepezil maintained Mini-Mental State Examination (MMSE) (Folstein et al. 1975) scores near baseline as compared with the placebo group, which deteriorated significantly. The longest placebo-controlled study (Courtney et al. 2004) was of 3 years' duration. In this trial, MMSE scores were better by 0.8 points at the end in the donepezil group than the placebo group, but there was no difference in scores on disability scales or rates of institutionalization.

In a report on donepezil administered for as long as 144 weeks it was found that, on average, cognitive scores for individuals who had received 10 mg/day remained above baseline for 51 weeks (Doody et al. 2001). However, this finding is of limited value because it was selective, only including patients who were benefiting from the medication.

Several reports have appeared indicating that donepezil is of value in late-stage Alzheimer disease (Feldman et al. 2005). A 24-week study of subjects in assisted living or nursing homes compared donepezil 10 mg/day versus placebo (Winblad et al. 2006a). Of the subjects, whose MMSE scores ranged from 1 to 10 at baseline, 128 were randomized to donepezil, 120 to placebo. There were 95 completers in the donepezil group and 99 in the placebo group. At 24 weeks, patients on active drug improved more on a test of cognitive function and declined less in a measure of activities of daily living than did those on placebo. The differences were small, but significant. A second 24-week study included subjects with MMSE scores ranging from 1 to 12. Of these, 176 were randomized to donepezil 10 mg/day, 167 to placebo (Black et al. 2007). Although there was essentially no improvement in performance of activities of daily living, there were small but significant differences in cognitive and global measures favoring donepezil.

Common side effects reported by patients include nausea, vomiting, diarrhea, muscle cramps (caused by nicotinic effects), mild stimulation, and vivid dreams at night that are sometimes frightening. Other less common potential side effects of donepezil include muscarinic cholinomimetic effects such as urinary urgency or incontinence, sweating, rhinorrhea, and syncope. The more common gastrointestinal side effects usually are transient and re-

spond to short-term abstinence from the drug or lowering of the dosage. Although there is slightly greater efficacy at 10 mg/day, there are significantly greater side effects at that dosage. Titration from 5 to 10 mg is recommended after 4–6 weeks; earlier increases in dosage are associated with more frequent side effects. Donepezil has low affinity in vitro for CYP2D6 and 3A4, making drug-drug interactions unlikely. Although the manufacturer recommends dosing the medication at bedtime, the stimulating effects of the drug (including vivid dreams) may be better tolerated if it is administered in the morning. Although not approved by regulatory authorities, some physicians will, as dementia inevitably worsens in the patient, titrate up to 15 or 20 mg/day. Patients and families should always be advised that while there is some chance of further temporary improvement in cognitive symptoms, the risk of adverse effects also increases with the higher dosages.

Rivastigmine

This drug, a carbamate marketed as Exelon, reversibly inhibits both acetylcholinesterase and butyrylcholinesterase. It is rapidly absorbed when taken orally and has the bioavailability of 0.36, but is only 40% protein bound. Elimination half-life is approximately 2 hours. It covalently binds to cholinesterases and breaking of these bonds converts rivastigmine to an inactive metabolite at the site of action. The parent compound is not metabolized by the liver (Jann 2000). Rivastigmine's effects are dose dependent. In a double-blind, placebo-controlled study of the drug in Alzheimer disease patients, dosages of 1–4 mg/day and 6–12 mg/day were compared with placebo in a 699-patient trial over 26 weeks (Corey-Bloom et al. 1998). Dosage was titrated upward weekly until the maximum tolerable dosage was reached. In the placebo and low-dosage groups the dropout rate was 15%, whereas in the high-dosage group the dropout rate was 35%. Only 55% of the persons in the high-dosage group achieved the maximum rivastigmine dosage of 12 mg/day. At 26 weeks, the high-dosage rivastigmine group differed from placebo group by nearly 5 points on the ADAS-Cog, remaining 1 point above baseline. At 26 weeks, the high-dosage rivastigmine group had improved 0.3 points over baseline on the MMSE, whereas the placebo-treated group had declined by 0.79 point. An ADL scale showed that 25% of high-dosage rivastigmine-treated patients had clinically meaningful improvement compared with 15% of persons in the placebo group. There was no difference in outcome between the low-dosage rivastigmine and placebo groups. Rösler et al. (1999) led a similar large double-blind, placebo-controlled parallel study showing a similar dropout rate for high-dosage rivastigmine. Using an intent-to-treat analysis, the proportion of high-dosage rivastigmine-treated subjects who achieved a meaningful improvement (4 points at study end point on the ADAS-Cog vs. baseline) was higher than in the placebo group (24% vs. 16%). Among those who completed the 26 weeks of study, the proportion was 29% versus 19%. The incidence of treatment-related side effects increased with rivastigmine dosage and decreased with dosage reduction in both studies. The most common side effects were cholinergic, including nausea, vomiting, diarrhea, and anorexia. Nausea and vomiting occurred most commonly in the dosage titration phase.

Rivastigmine was originally available in capsules of 1.5, 3, 4.5, and 6 mg. The drug is administered twice a day with food. The initial recommendation of the manufacturer was titration of the drug at a minimum 2-week interval per each dose up to 6 mg twice a day. However, clinical experience indicates that fewer side effects were encountered with dosage titration at 4-week intervals, and it is now suggested that the medication be taken after a full meal. Even with these modifications, nausea, vomiting, and diarrhea tend to limit dosing such that the majority of patients are unable to reach the 12-mg/day dosage. For this reason a transdermal patch has been developed, and in a double-blind, placebo-controlled, double-dummy study of over 1,000 patients with mild to moderate Alzheimer disease that also compared against rivastigmine capsules, it was found that 80% of subjects tolerated the intermediate-dose, 9.5 mg/24-hour patch, which is bioequivalent to 6-mg capsules two times a day. This dosage patch group had two-thirds less cholinergic gastrointestinal side effects than did the capsule group. The 24-hour transdermal patch is now available in dosages of 4.6 and 9.5 mg/24 hours (Cummings and Winblad 2007). There are few gastrointestinal side effects with this preparation and skin irritation is relatively rare. Clinical experience suggests that transition from capsule to patch requires no delay between dosages ranging from 1.5 to 3 mg two times a day to the 4.6-mg patch. Patients receiving 4.5 or 6 mg two times a day readily can be switched to the 9.5-mg patch. The rivastigmine patch largely has replaced the use of capsules in clinical practice.

Galantamine

Galantamine is an alkaloid derived from the bulbs of the snowdrop variety of daffodil and was first marketed as Reminyl and more recently, because of name confusion with other products, as Razadyne. Galantamine reversibly and competitively inhibits acetylcholinesterase (Bores et al. 1996). It also modulates allosterically the response of nicotinic receptors to acetylcholine. The enhancement of cholinergic nicotinic neurotransmission may increase release of acetylcholine (Albuquerque et al. 1997). This is

theoretically of potential clinical importance for the therapy of Alzheimer disease, in which there is a significant loss of cortical nicotinic acetylcholine receptors (Court et al. 2001). However, there is no evidence that this mechanism contributes to the observed therapeutic actions of galantamine.

Galantamine is well absorbed and has absolute bioavailability of about 90%. It has a terminal elimination half-life of 7 hours and has linear pharmacokinetics in dosages from 8–32 mg/day. It is 18% protein bound. The drug is metabolized by the hepatic P450 isoenzymes and by glucuronidation, and it is also excreted unchanged in the urine.

Raskind et al. (2000) conducted a 6-month randomized, placebo-controlled trial in 636 subjects with mild to moderate Alzheimer disease. Patients were randomized to placebo or to escalating dosages of galantamine up to 24 or 32 mg/day. (Eligible subjects also entered a 6-month open-label study of the 24-mg/day dosage.) Patients receiving either dosage of drug had significantly improved ADAS-Cog scores as compared with those receiving placebo (patients receiving 24 mg/day scored 3.9 points higher on average than the placebo group; patients receiving 32 mg/day scored 3.8 points higher), and both groups showed significantly better scores than the placebo group on the Clinician's Interview-Based Impression of Change Plus Caregiver Input) (CIBIC-Plus) (Schneider et al. 1997). At 12 months on the 24-mg/day dosage, ADAS-Cog scores and daily function showed no deterioration from baseline.

Wilcock et al. (2001) reported on a double-blind, placebo-controlled study of 653 persons with mild to moderate Alzheimer disease whose daily dose of galantamine was escalated weekly over 3–4 weeks to 24 or 32 mg/day. The dropout rates for adverse events were 13.5% for the placebo group, 20% for the 24-mg group, and 22% for the 32-mg group. ADAS-Cog scores differed significantly from placebo at 6 months (2.9 points different for 24 mg; 3.1 points difference for 32 mg) based on an intent-to-treat analysis. Apolipoprotein E genotype had no effect on outcome. Titration at monthly intervals in a third study (Tariot et al. 2000) reduced the dropout rate for adverse events to 7% for 16 mg/day and 10% for 32 mg/day. In this study, there were significant differences in scores on the CIBIC-Plus, on ADL, and on behavioral symptoms, assessing with the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994). Adverse events in all studies were primarily gastrointestinal symptoms. On the basis of these studies, the manufacturer recommended titration to 16 or 24 mg/day (8- or 12-mg capsules two times a day) at 1-month intervals. It has been available in 4-, 8-, and 12-mg capsules that were administered two times a day. A recent study investigated use of 8-mg, 16-mg, and 24-mg extended release capsules dosed once per day in the morning. The effective area under the curve was similar to twice-daily dosing with half-life extended to 4.4 hours (Zhao et al. 2005). This study revealed comparable adverse effects and efficacy to the immediate release form of the medication. An extended release form is now available that allows once-per-day dosing of 8, 12, and 24 mg, usually taken in the morning. The manufacturer suggests that the extended release capsules be taken with food. The extended release once-per-day form of galantamine largely has replaced the immediate release form in clinical practice.

Head-to-Head Comparisons

A number of head-to-head comparisons have been made between cholinesterase inhibitors. In a 12-week, open-label study in 111 outpatients with mild to moderate Alzheimer disease, subjects were treated with donepezil 10 mg/day or rivastigmine up to 6 mg two times a day. There were fewer dropouts in the donepezil (11%) than in the rivastigmine group (31%), and a greater percentage of the donepezil group (88%) were able to tolerate the maximum dose of drug, whereas only 47% of rivastigmine-treated patients were able to achieve the maximum dose. Cognitive effects (approximately 1-point gain in MMSE score) were similar for both groups at 12 weeks (Wilkinson et al. 2002). In a 994-patient, double-blind study of rivastigmine versus donepezil, adverse events and dropout rates were slightly higher in the rivastigmine group, whereas there were no differences in cognition, ADLs, or behavior as measured by the various scales employed (Bullock et al. 2005). In a 52-week parallel group study, galantamine was compared with donepezil. Galantamine subjects were started at 4 mg twice per day and titrated up to 12 mg two times a day if tolerated; those on donepezil were titrated to 10 mg/day if tolerated. At study end, there were no differences between study groups on an ADL scale. There was a modest but insignificant difference in MMSE scores favoring the galantamine group (reduction of 0.52 point from baseline for galantamine vs. a 1.58 point loss for donepezil) (Wilcock et al. 2003). In general, these studies must be judged with caution given the conflict of interest for the sponsoring company designing the trial. Nonetheless, most studies have shown relative equivalence in efficacy for these drugs.

Switching Anticholinesterases

Despite lack of difference in clinical efficacy, there have been studies suggesting that patients who do not tolerate or appear to be losing ground taking one cholinesterase inhibitor may benefit from change to another drug of the

same class. For example a 6-month, open-label study evaluated the safety and efficacy of rivastigmine in 382 Alzheimer patients who had failed to benefit from donepezil (80% from lack of efficacy, 11% from tolerability problems, and 9% from both) (Auriacombe et al. 2002). At the end of the study, 56% of patients had responded to rivastigmine on both global and cognitive measures. Contrary to the clinical experience of others, these investigators found that having had side effects from donepezil did not predict similar problems with rivastigmine. Issues of appropriate comparator baseline and of what constitutes a clinically significant response both cloud interpretation of the results for this study. In general it is reasonable to try a second cholinesterase inhibitor if the family, patient, or clinician believes the first drug is ineffective or the benefits from the medication are failing and or if there are significant adverse effects. Results with the second drug may be better, the same, or worse than the first. When progressive disease with worsening symptoms obscures any beneficial effects, a consensus decision between the patient, family, or caregiver and physician should be made regarding the cost and benefits of therapy and whether to continue it.

Anticholinesterases for Behavioral and Psychological Symptoms

To test the theory that the delusions of Alzheimer disease might be caused by a cholinergic deficit in the limbic system, Cummings et al. (1993) administered oral physostigmine to two Alzheimer patients. Following drug dosing of 1 mg approximately every 2 hours (because of the short half-life of physostigmine), delusions were markedly diminished. Later, Cummings and Kaufer (1996) and Cummings and Back (1998) postulated that a variety of neuropsychiatric symptoms in Alzheimer disease might be related to cholinergic deficits and might respond to cholinergic treatment. Cummings (2000) suggested that acetylcholinesterase inhibitors should be considered psychotropic drugs and that loss of input from cholinergic neurons in the basal forebrain to the limbic and paralimbic regions and to the cerebral cortex might be the underlying mechanisms connecting behavior and psychiatric symptoms to the cholinergic system.

Raskind et al. (1997) reviewed behavioral assessment data from a 30-week tacrine trial using last observation carried forward. They compared outcomes for 181 persons receiving placebo and 234 persons receiving tacrine in dosages ranging from 40 to 160 mg/day. They found that on 3 of the 10 ADAS noncognitive items (cooperation, delusions, and pacing), there were significant improvements with tacrine over placebo. In a different open-label study of tacrine in outpatients with Alzheimer disease, there was significant reduction in total NPI scores with the moderately impaired subject group showing greater improvement than mildly or severely impaired subjects (Kaufer et al. 1998).

Mega et al. (1999) studied 86 community-dwelling persons with Alzheimer disease who were treated with donepezil 5 mg/day for 4 weeks, followed by treatment with 10 mg/day for 4 weeks. Using global NPI scores as the criterion, behavioral improvement was seen in 41% and behavioral worsening in 28%. Persons who showed behavioral responses had worse initial scores on the following NPI subscales: delusions, agitation, depression, anxiety, apathy, disinhibition, and irritability. Cummings (2000) reported on 84 persons with Alzheimer disease treated with donepezil for 6 months and contrasted them with a group of Alzheimer disease patients ($n = 248$) who were not taking the drug. Patients taking donepezil were significantly less likely to be threatening, destroy property, or talk loudly, and fewer were receiving sedatives. Weiner et al. (2000) performed a prospective 12-month study of donepezil in 25 Alzheimer disease patients compared with a reference group of community-dwelling persons with Alzheimer disease who were not receiving anticholinesterase treatment ($n = 153$) and were enrolled in a 1-year study of assessment instruments for Alzheimer disease patients (Patterson et al. 1997). Using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavioral Rating Scale for Dementia (CBRSD), Tariot et al. (1995) found that the donepezil-treated group showed improvement in CBRSD total scores at 3 months and in depression and behavior dysregulation scores at 4 months. In this group, CBRSD total, depression, and behavioral dysregulation scores returned to baseline at 12 months, in contrast with the reference group, whose CBRSD scores worsened minimally over the 12 months.

Patients diagnosed as having dementia with Lewy bodies based on neuropathological examination are usually found to have both widespread amyloid plaques and neurofibrillary tangles typical of Alzheimer disease as well as Lewy bodies. In an open-label study of rivastigmine in 11 persons diagnosed clinically with dementia with Lewy bodies, neuropsychiatric inventory scores fell after 12 weeks of treatment by 73% for delusions, 63% for apathy, 45% for agitation, and 27% for hallucinations. Of the 11 persons treated, 5 had not responded to prior treatment, including with low-dose neuroleptics. Furthermore, parkinsonian symptoms tended to be improved. The mean dosage of rivastigmine was 9.6 mg/day (range, 3–12 mg/day) (McKeith et al. 2000a). A larger ($n = 120$) double-blind, placebo-controlled study was conducted over 20 weeks in patients with dementia with Lewy bodies. Of the 120 participants, 18 taking rivastigmine and 10 taking placebo

dropped out. The mean dosage of rivastigmine of 9.4 mg/day at the end of the 8-week titration period declined slightly afterward. The maximum daily dosage of 12 mg was achieved by 56% of the 48 completers; most (92%) were able to tolerate at least 6 mg/day. There was no change in extrapyramidal symptoms when patients were taking rivastigmine. Despite the lack of significant differences at 20 weeks between rivastigmine and placebo in MMSE and Clinical Global Change scores, patients receiving rivastigmine were significantly less anxious and apathetic and had fewer delusions and hallucinations than control subjects (McKeith et al. 2000b). A later report from this same study indicated that therapeutic benefits were lost when the drug was discontinued after 20 weeks (Wesnes et al. 2002), underscoring the need to maintain treatment with cholinesterase inhibitors. Ringman and Simmons (2000) reported successful treatment of three cases of rapid eye movement sleep behavior disorder with donepezil.

Although there is much reporting of salutary behavior effects from cholinesterase inhibitors, these are generally uncontrolled case series or retrospective subanalyses. These patients often had little behavioral disturbance at baseline, and the clinical significance of any apparent differences is not clear. The responsiveness of the persons with greater symptoms may be a function of having scores high enough on behavioral instruments to be detected, and their improvement as regression to the mean (Cummings et al. 2004).

Real-World Therapy Using Anticholinesterases

The cholinesterase inhibitors should be used with caution in persons with complete heart block or sinus bradycardia and in the presence of active peptic ulcer disease, asthma, or chronic obstructive pulmonary disease. However, drug-drug interactions are uncommon. Patients and their families do need to be counseled about the concomitant use of highly anticholinergic drugs such as diphenhydramine, oxybutynin, and dicyclomine.

In our practice, we offer cholinesterase inhibitors to patients whom we believe to be in the prodromal stage of Alzheimer disease and have not reached the stage of full-blown dementia and to patients with mild or moderate Alzheimer disease. We also offer these drugs to patients who appear to have a vascular component to their symptoms in addition to Alzheimer disease based on studies showing that patients with clinically diagnosed vascular dementia responded similarly to those with Alzheimer disease. Both vascular dementia and mixed vascular dementia and Alzheimer disease groups treated with galantamine showed beneficial treatment responses (Erkinjuntti et al. 2002). In our experience, vascular or mixed dementia subjects invariably have at least moderate Alzheimer pathology at autopsy. We generally attempt to reach the maximum dosage suggested by the manufacturer in all dementia subjects regardless of the specific diagnosis because the beneficial effects of these drugs are dose related. Our hope is to maintain the patient's level of function in activities of daily living as long as possible. In dealing with families, we emphasize that mild improvement, stabilization, or slowing of progression are all good outcomes. It is difficult to know how long treatment should be continued, because it is difficult to distinguish loss of drug effect from progression of the disease, and with discontinuance of therapy there may be worsening of symptoms. When the decision is made to discontinue a cholinesterase inhibitor, gradual downward dosage titration seems appropriate; our experience is that rapid withdrawal is often followed by an exacerbation of cognitive and behavioral symptoms. If symptoms worsen with slow withdrawal, we restart or continue the cholinesterase inhibitor. In the later stages of dementia, when patients no longer know or interact in a meaningful way with family or caregivers, we believe there are no longer any meaningful benefits to the patient or their family and with family's consent will discontinue therapy at this time.

N-Methyl-D-Aspartate Receptor Antagonists

Memantine

This *N*-methyl-D-aspartate (NMDA) receptor antagonist, marketed as Namenda, blocks the actions of glutamate at this site, improving synaptic transmission and/or preventing calcium release, which may provide neuroprotection. It has been used in Germany since the 1980s as a therapy for organic brain syndrome. Memantine is well absorbed and has a 70-hour or greater half-life but is still given two times a day because that was the dosage scheme used prior to studies establishing efficacy in the late 1990s.

A 12-week multicenter European study of nursing home patients with moderate-to-severe stage Alzheimer dementia or vascular dementia treated with placebo compared with memantine 10 mg/day demonstrated delay in symptomatic cognitive and functional deterioration. Memantine-treated patients also were significantly less dependent on nursing staff. In a large double-blind, placebo-controlled U.S. study of memantine 20 mg/day of 12-week duration in moderate to severe stage Alzheimer disease patients, similar benefits were seen in delaying cognitive loss and deterioration in functioning in ADLs. Meman-

tine-treated patients also required significantly less caregiver time. In clinical practice, memantine is helpful in moderate- and severe-stage Alzheimer patients, with dosing started at 5 mg/day, titrated up 5 mg/day each week to a final dosage of 10 mg two times a day. There may be transient confusion or sedation during the titration phase, but memantine generally has had fewer adverse effects than the cholinesterase inhibitors in clinical practice (see Table 18–2). Two large double-blind, placebo-controlled studies of memantine in mild-stage patients have shown minimal or borderline results in efficacy assessments. Nonetheless, frequently it is used in these patients with variable efficacy but with good results in some patients. A major issue is often the cost of the off-label use of the drug.

Combination Therapy With Cholinesterase Inhibitors and Memantine

Because cholinesterase inhibitors and memantine have different mechanisms of action, the rationale is therefore strong that combination therapy may give additional benefits as compared to treatment in Alzheimer disease with either drug alone.

A large double-blind, placebo-controlled trial of memantine has been conducted in subjects on established stable doses of donepezil, with average duration of preceding cholinesterase inhibitor therapy being 24 months. Patients on donepezil plus memantine were more likely to complete the trial, had fewer gastrointestinal adverse effects, and had improved global functioning, cognition, function in ADL, and behavior as compared with subjects on stable doses of donepezil plus placebo. Open label studies of galantamine or rivastigmine plus memantine have had similar outcomes.

Combination of a cholinesterase inhibitor with memantine has become the preferred treatment in clinical practice for moderate to severe Alzheimer patients except as limited by adverse effects and/or the financial burden of paying for two cognitive enhancers.

Serotonin Augmentation

Cell loss in Alzheimer disease often occurs in the dorsal raphe nucleus of the brainstem, the site of serotonergic innervation of the forebrain (Yamamoto and Hirano 1985). As a result, the brain serotonin metabolites are reduced by 30%–40% (Gottfries et al. 1983). The relationship between the serotonergic system and cognition in Alzheimer disease is unclear, but clinical experience suggests that serotonergic augmentation modestly may increase functional performance. This belief is supported by two recent double-blind, placebo-controlled studies in patients with MCI and mild- to moderate-stage Alzheimer disease. In the MCI study, subjects treated with fluoxetine had slightly improved memory and cognition as compared with a placebo group (Mowla et al. 2007b); in the Alzheimer study, patients treated with fluoxetine and rivastigmine did better in their ADLs and global functioning than those treated with rivastigmine alone or placebo (Mowla et al. 2007a).

The most successful serotonergic strategy has been the use of selective serotonin reuptake inhibitors (SSRIs). This class of drugs includes fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro). Paroxetine (Paxil) is another member of this class but should be avoided because of anticholinergic side effects. SSRIs are the most commonly prescribed class of antidepressants in elderly subjects because of their relative lack of life-threatening or other unpleasant side effects and once-per-day dosing. These drugs are administered in the morning because of their mild stimulating effects. Transient increase in anxiety, sleeplessness, loss of appetite, diarrhea, and sexual dysfunction (inhibited orgasm or ejaculation, loss of libido) may occur with all drugs of this class.

Fluoxetine is virtually devoid of anticholinergic, antihistaminic, or antiadrenergic side effects (Harris and Benfield 1995). It does occasionally have antidopaminergic actions that can be associated with extrapyramidal adverse effects in some patients. It has been widely used in elders, but it has been associated with weight loss in nursing home patients (Brymer and Winograd 1992) and with the syndrome of inappropriate antidiuretic hormone secretion (Druckenbrod and Mulsant 1994). Sleep disturbance and increased agitation have also been reported. Its long half-life (1–3 days), presence of an active metabolite, and its potent inhibition of cytochrome P450 CYP2D6 and intermediate inhibition of CYP3A4 can result in drug accumulation. Therefore, low doses or less than daily dosing should be considered in treating very frail elderly patients with dementia. Fluoxetine is administered at a dosage of 5–20 mg/day, but this may be reduced if it is overly stimulating by giving one capsule every other day or fluoxetine concentrated solution.

Sertraline has a 24-hour half-life. It is a weak inhibitor of CYP3A4 and CYP2D6. Transient nausea may rarely occur with its use. The drug appears to be well tolerated by the elderly (Cohn et al. 1990). Dosing in older outpatients is either 50 or 100 mg/day, starting at 50 mg/day; in frail elders dosing begins at 25 mg/day. There is little evidence that dosages greater than 100 mg/day are more effective than dosages of 50–100 mg/day. Dose escalation often is desirable over time to avoid adverse effects.

TABLE 18–2. Percent of adverse events (5% or over) associated with the use of ChEIs and memantine in patients with Alzheimer disease

Adverse event	Donepezil, oral	Rivastigmine, oral	Rivastigmine, transdermal	Galantamine, oral	Memantine, oral
	n=747	*n*=1,189	*n*=291	*n*=1,040	*n*=940
Abdominal pain		**13**		5	
Accident	**7**	**10**			
Anorexia		**17**		**9**	
Anxiety		5			
Asthenia		6			
Confusion		8			**6**
Constipation		5			**5**
Depression		6		**7**	
Diarrhea	**10**	**19**	**6**	**9**	
Dizziness	**8**	**21**		**9**	**7**
Dyspepsia		**9**		5	
Fatigue	**5**	**9**		5	
Headache	**10**	**17**		8	6
Insomnia	**9**	**9**		5	
Malaise		5			
Muscle cramps	**6**				
Nausea	**11**	**47**	**7**	**24**	
Pain	**9**				
Somnolence		5			
Urinary tract infection		7		**8**	
Vomiting	**5**	**31**	**6**	**13**	
Weight decrease				**7**	

Note. The amounts above represent adverse events (AEs) reported in at least 5% of the patients receiving the drug and at a higher frequency than placebo-treated patients (the 10 most frequently occurring AEs for each drug are indicated in bold). Because of differences in trial design, the percentage of AEs for each drug should not be directly compared with each other, but they do give a perspective of which AEs are more likely to occur with each drug. Information comes from manufacturers' package inserts. ChEIs = cholinesterase inhibitors.

Citalopram and its S-isomer escitalopram are the most serotonin-selective of the SSRIs (Owens et al. 1997). These drugs are well tolerated in elderly subjects with Alzheimer disease. Citalopram is initiated at 20 mg/day, and escitalopram is dosed initially at 10 mg/day.

Serotonin Syndrome

The serotonin syndrome may be seen occasionally with all of the SSRIs and has been recently reviewed by Isbister et al. (2007). It is a rare complication but more common when combinations of drugs are employed. In particular, combinations of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, MAOIs and SSRIs, and MAOIs and venlafaxine (Effexor) are the most commonly reported causes. The full-blown serotonin syndrome includes mental status changes, agitation or restlessness, myoclonus, hyperreflexia, diaphoresis, tremor, shivering, incoordination, autonomic dysfunction, hyperthermia, and muscular rigidity. Myoglobinuria and renal failure may result, as may seizures or disseminated intravascular clotting. Treatment of serotonin syndrome entails withdrawal of the precipitating drug.

Selective Serotonin Reuptake Inhibitor Withdrawal

Withdrawal symptoms are common when SSRIs are discontinued, even when they are tapered slowly. Such symp-

toms tend to be more common with SSRIs with shorter half-lives, such as paroxetine, than with sertraline or fluoxetine. The symptoms persist up to 21 days and most commonly include dizziness, lethargy, paresthesia, nausea, vivid dreams, irritability, and depressed mood. They are relieved, usually within 24 hours, by restarting the medication (Lader 2007) and are not relieved by benzodiazepines.

Antioxidants

Evidence of possible central nervous system damage because of lipid peroxidation and oxidative injury (Lethem and Orrell 1997; Sano et al. 1996) led to a trial of vitamin E (α-tocopherol) and the MAOI selegiline double-blind and placebo-controlled trial in 341 persons with moderate- to severe-stage Alzheimer disease (Sano et al. 1997). The trial, conducted over 2 years, compared α-tocopherol (2,000 IU/day), selegiline (10 mg/day), and α-tocopherol plus selegiline with placebo. The primary outcome measure (end point) was time to death, institutionalization, loss of ability to perform basic activities of daily living, or severe dementia (CDR score of 3). When adjusted for severity of illness at the beginning of the study, selegiline was associated with a delay of 655 days to end point; α-tocopherol, 670 days; and selegiline and α-tocopherol combined, 585 days. Progression to end point appears to be delayed about 25% versus placebo. There was no difference between groups in cognitive measures or in overall side effects. The most important contraindication to high-dose vitamin E is the use of warfarin (Coumadin) as an anticoagulant. For many years, 2,000 units of vitamin E were prescribed widely in patients with MCI and Alzheimer disease. However, a later 1-year, double-blind, placebo-controlled transdermal patch study of high-dose selegiline failed to show any benefit over placebo (Farlow et al. 1999). With regard to vitamin E, recent studies have suggested an increase in potential for abnormal blood clotting above 1,000 IU (Petersen et al. 2005), and the vitamin E group, in a large 3-year MCI study, failed to show any cognitive benefits versus placebo. For these reasons use of vitamin E as a neuroprotective agent by practitioners treating MCI and Alzheimer disease has diminished greatly.

Flavonoid extracts of the leaves of the Ginkgo biloba (maidenhair) tree are available on a nonprescription basis throughout the world for a variety of nonspecific indications, including an implicit claim of improving memory in healthy persons as well as those with disorders affecting memory. The substance may have antioxidant and anti-inflammatory properties (Oken et al. 1998). In a mouse model of Alzheimer disease, Ginkgo biloba has inhibited amyloid beta (Aβ) oligomerization, protected neurons against Aβ toxicity, and enhanced adult hippocampal neurogenesis in addition to improving cognitive deficits (Tchantchou et al. 2007).

A 6-week, randomized, placebo-controlled study in healthy cognitively intact elders showed no effect on cognitive measures at a dosage of 40 mg three times per day (Solomon et al. 2002). A 52-week randomized, double-blind clinical trial was performed in the United States involving persons with Alzheimer disease and vascular dementia (LeBars et al. 1997). Patients were dosed at 40 mg three times per day with EGb 761, a pharmaceutical-grade, standardized extract of ginkgo flavonoids. Of 309 persons enrolled, 52-week data were available for 202 persons. In an intent-to-treat analysis, the Ginkgo-treated group had scores on the cognitive subscale of the ADAS-Cog that were 1.4 points better than those of the placebo group (P=0.004). In the Alzheimer disease subgroup (n=236), the difference was 1.5 points. No difference was detected on the Clinical Global Impression of Change scale. The drug did not differ significantly from placebo in side effects. An analysis by Oken et al. (1998) of Ginkgo biloba studies concluded that only four (including that of LeBars et al. 1997) met criteria for meta-analysis. In general, there was a small but significant effect in Alzheimer disease patients at 3 and 6 months with 120–240 mg/day, which amounted to a 3% difference in the ADAS-Cog scores between drug and placebo. Mazza et al. (2006) performed a 24-week head-to-head trial comparing EGb 761 dosed at 160 mg/day with the cholinesterase inhibitor donepezil 5 mg/day and with placebo in subjects with Alzheimer disease. Patients were age 50–80 years and had mild to moderate dementia. In this study, EGb 761 was comparable in efficacy to donepezil. Finally, Schneider et al. (2005) performed a large multicenter, double-blind, placebo-controlled trial of EGb 761 in 600 patients with mild- to moderate-stage Alzheimer disease. No benefits were seen over the 6-month course of the study in cognition, ADLs, or behavior.

Although Ginkgo biloba is still used widely by elderly patients with and without memory problems, as well as Alzheimer disease patients, the evidence suggests it has a modest to no effect on cognitive function. On the positive side, this drug appears to cause very few side effects.

Treatment of Mild Cognitive Impairment

A recent review found three published and five unpublished randomized, double-blind, placebo-controlled trials of acetylcholinesterase inhibitors in MCI patients; three with donepezil, two with rivastigmine, and three with galantamine (Raschetti et al. 2007). The trials ranged from 24

weeks to 3 years. Over these periods of time, no significant difference occurred in the probability of conversion from MCI to dementia between active treatment and placebo groups. The best known of these trials compared the transition from MCI to dementia in persons treated with donepezil 10 mg/day, vitamin E 2000 IU/day, and placebo over 3 years (Petersen et al. 2005). During the first 12 months, conversion from MCI to dementia was significantly lower in the donepezil group, but at 3 years there was no difference between any of the groups. It is of interest that apolipoprotein ε4 subjects in this study were significantly more likely to convert to Alzheimer disease and that donepezil treatment in this subgroup was significantly more likely to delay progression to dementia. The shorter donepezil trials have suggested modest symptomatic benefits in some patients documented by some assessment measures but not others. The largest published rivastigmine study, which enrolled over 1,000 patients who were followed for 4 years, was negative. The galantamine MCI trials had an excess of deaths in the galantamine-treated groups, or, more correctly, there were fewer deaths in the placebo group than has been previously seen in similar trials, perhaps by chance. MCI has not been accepted by the FDA as a treatment indication, primarily because of ambiguity regarding the specificity of the diagnosis. In practice, many physicians treat MCI as the mildest stage of Alzheimer disease and do offer cholinesterase inhibitor therapy as a possible choice for their patients.

Conclusion

The cholinesterase inhibitors have been demonstrated to mildly improve cognition and functioning in ADLs across mild to severe stages of Alzheimer disease. They tend to be most effective at their maximum tolerated dosage. Dosing is typically limited by adverse gastrointestinal effects. Their actions are symptomatic. Benefits, which are typically modest, may not be seen in many patients. More recently, memantine, a partial antagonist at the NMDA receptor has been demonstrated to mildly improve cognition and activities of daily living in Alzheimer subjects with moderate to severe stage dementia, and these benefits may be additive to the effects of cholinesterase inhibitors. Other commonly used drugs such as ginkgo biloba and the antidepressants have much less secure evidence supporting their use. There remains a major need for drugs that will actually slow biological progression of the disease. Many agents with such actions primarily directed at accelerating removal, preventing formation, and or deposition of amyloid into plaques of the brain are being investigated, as indicated in Chapter 26 of this volume, "Prevention of Dementia and Cognitive Decline." The next few years hold promise if these new therapies prove successful, or they require a major reconsideration of which are the real mechanisms underlying Alzheimer disease if the trials fail. Other therapeutic trends such as increasing exercise, reducing body weight, and/or aggressively treating the metabolic syndrome increasingly are being recommended by physicians to reduce vascular disease and or Alzheimer disease, although objective evidence that these efforts will be effective clinically are years away. For now, treatment with a cholinesterase inhibitor and/or memantine with psychotropic drugs added as needed to treat behavioral symptoms remain the therapeutic approach most likely to achieve the best clinical outcome in patients with Alzheimer disease or other related dementias.

KEY POINTS

- The two classes of FDA-approved cognitive enhancers for Alzheimer disease are acetylcholinesterase inhibitors and NMDA antagonists.
- Cholinesterase inhibitors in the more current dosage forms are comparable to each other in efficacy and adverse effect rates.
- These drugs have modest efficacy and have not been shown to delay progression of the illness.
- Careful attention must be paid to comorbid conditions and titration when initiating therapy with these drugs.

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CHAPTER 19

Management of Advanced Dementia

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Joyce Simard, M.S.W.

In this chapter we describe the current evidence for best practices in the care of advanced dementia. Most cases of late-stage dementia are caused by Alzheimer disease, cerebrovascular disease, disorders associated with Lewy bodies, and the frontotemporal dementias. Although symptoms of these diseases differ early on, problems facing the patients and their caregivers are very similar in the late stage. Their similarity may also be related to the finding that more than one cause of dementia contributes to the symptoms shown in Figure 19–1. In a series of 226 postmortem examinations of individuals who died on a dementia special care unit, Alzheimer disease was the sole diagnosis in 47% and was combined with other diagnoses in 62%. Dementia with Lewy bodies was the second most common diagnosis, occurring in 19.4% of cases, exactly one-half (9.7%) concomitant with Alzheimer disease. Parkinson disease, a Lewy body spectrum disorder, was found in only 1.3% of cases, usually in combination with significant vascular disease. Vascular pathology sufficient to cause dementia was found in 13.7%, also frequently in association with other disorders. The frontotemporal degenerations accounted for 10% of postmortem diagnoses. Classic Pick disease was encountered in 1.3% of autopsies, corticobasal ganglionic degeneration in another 1.3%, and frontal lobe degeneration in 2.2%. Other disorders, including progressive supranuclear palsy and Huntington disease, were found in the remaining 5.3% of cases (Volicer et al. 2001).

Despite advances in our understanding of the pathogenesis of these disorders, they are at the present time both progressive and irreversible. Because the prevalence of dementia increases with age and the number of people surviving to old age is growing, management of late-stage dementia is becoming increasingly important at a personal and societal level. The cost of care increases with dementia severity largely because many individuals require institutional care (Jönsson et al. 2006). Maintaining persons with late-stage dementia at home may provide greater comfort but may cost more than institutional care (Grabowski 2006). However, there is evidence that providing palliative care for institutionalized advanced dementia patients may decrease cost of care and increase comfort for the patient (Volicer et al. 1994a). Currently, many nursing home residents are exposed to invasive, painful interventions before death, including tube feeding, laboratory tests, and intravenous therapy requiring restraints (Mitchell et al. 2004a), that may not be appropriate for their care. There are many published guidelines for de-

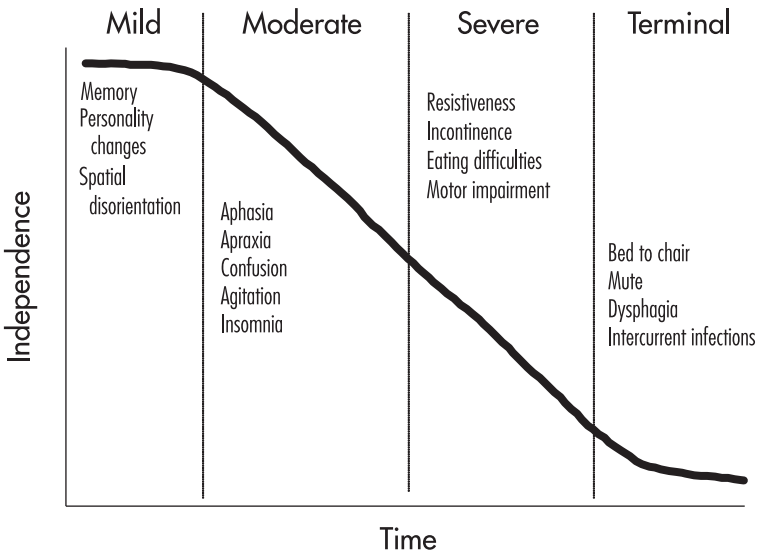

FIGURE 19–1. Course of Alzheimer disease and other progressive dementias.

mentia care. Of these, 24 were recently reviewed for their end-of-life care content (Mast et al. 2004). The best guidelines have been issued by the American Medical Association (1999), the American Psychiatric Association (1997), the Alzheimer's Association of Los Angeles, Riverside, and San Bernardino Counties (California Workgroup on Guidelines for Alzheimer's Disease Management 2002), and the American Medical Directors Association (1998).

Definition of Advanced Dementia

The most common terms used to stage dementia are *mild, moderate,* and *severe.* The term *severe dementia* often is used in the literature but does not have a generally accepted definition. The original version of the Clinical Dementia Rating Scale (Hughes et al. 1982) used the stages of mild, moderate, and severe, but the individuals rated as severe still retained significant function. This resulted in adding two further stages, *profound* and *terminal,* to cover the whole spectrum of dementia progression (Dooneief et al. 1996). In contrast, the Functional Assessment Staging rating scale uses *severe* as the category at which patients lost almost all language and mobility (Reisberg 1988).

The term *advanced dementia* is not used in any rating scale but is often used in the research literature without being clearly defined. The Joint Commission considers advanced dementia equivalent to the Alzheimer's Association definition of *late stage,* when the person is typically incontinent, often bedridden, and may have difficulty with seizures, swallowing, infections, and communication (Joint Commission 2002). The Maryland legislature considers advanced dementia as an end-stage condition "an advanced, progressive, irreversible condition caused by injury, disease, or illness that has caused severe and permanent deterioration indicated by incompetency and complete physical dependency; and for which, to a reasonable degree of medical certainty, treatment of the irreversible condition would be medically ineffective." This law specifies that *end-stage condition* differs from *imminent death* and *persistent vegetative state* (Curran et al. 2000).

A detailed definition of advanced dementia is also provided in the Guidelines for Palliative Approach in Residential Aged Care published by the Australian Government (Australian Government, Department of Health and Aging 2006). It states that "advanced dementia, also known as 'late stage' or 'severe' dementia, is a neurological disease characterised by severe cognitive decline of an irreversible nature. It is associated with poor prognostic factors such as swallowing impairment, weight loss, dysphagia, anorexia, and bowel and bladder incontinence, and often results in the person being bedridden. The progression from diagnosis of advanced dementia to death is usually 3 years, and poorer prognosis is likely if the resident develops an acute illness such as pneumonia or another infectious disease."

For purposes of this chapter, dementia will be considered to have four stages: mild, moderate, severe, and terminal (Figure 19–1). Moderate dementia is when a person requires assistance with activities of daily living, severe

TABLE 19–1. Comorbidity in dementia patients and healthy elderly control subjects

Comorbidity	Dementia patients (%)	Control subjects (%)
Cerebrovascular disease	38.9	9.9
Congestive heart failure	29.3	14.0
Chronic obstructive pulmonary disease	24.9	19.8
Diabetes	21.8	16.1
Peripheral vascular disease	15.9	8.5
Myocardial infarction	13.0	5.4
Malignancy	12.1	10.1
Renal disease	8.3	3.2

Source. Adapted from Hill et al. 2002.

dementia is when the person becomes unable to ambulate and eat without assistance, and terminal is when the person cannot ambulate and becomes unable to communicate verbally. Advanced dementia will be considered as both the severe and terminal stages.

Medical Issues

Two types of medical issues must be addressed when caring for individuals with advanced dementia: 1) comorbid conditions and the consequences of dementia and 2) secondary conditions. Retrospective analysis of administrative data for 3,934 patients with dementia and 19,300 age- and sex-matched control subjects enrolled in a large Medicare managed care organization showed that comorbid conditions are very common in persons with dementia, with some more common than in matched cognitively intact elders (Hill et al. 2002) (Table 19–1). Three important principles apply to the management of comorbid conditions:

1. The inability of persons with advanced dementia to report symptoms of their diseases or side effects of treatment makes it important to treat chronic conditions such as hypertension and diabetes more conservatively to avoid overtreatment (e.g., postural hypotension, hypoglycemia).
2. Because advanced dementia decreases life expectancy, interventions that have only a long-term effect, such as treatment with cholesterol-lowering agents, are not appropriate.
3. It is important to keep in mind that painful medical interventions may cause behavioral problems in persons who do not understand the need for these interventions and cannot communicate their discomfort in words.

The most common secondary conditions are depicted in Figure 19–2. The most important are infections and eating difficulties, with aspiration as a common link. Similarly, constipation and pressure ulcers may be linked to infections and eating difficulties. Infections, constipation, and pressure ulcers may cause pain that also influences eating. Secondary conditions not listed in the figure are seizures and myoclonus that occur in some individuals with advanced dementia. Most individuals with dementia die from pneumonia, renal failure, or dehydration, and often they have burdensome symptoms while they are conscious (Brandt et al. 2006a). Suffering before death is especially common in countries in which a palliative approach to end-of-life care is not used (Aminoff and Adunsky 2006).

Infections

The most common infections in late-stage dementia involve the urinary tract, upper respiratory tract, lower respiratory tract, skin, gut, and eyes (Perls and Herget 1995). These infections are an almost inevitable consequence of advanced dementia for several reasons, including reduced immune responses (Ahluwalia and Vellas 2003). Risk of urinary tract infections is increased by incontinence in women and urinary retention in men (Brown 2002). Swallowing difficulties with aspiration increase the risk of developing respiratory infections (Janssens and Krause 2004), and the inability to ambulate increases risk for urinary and respiratory infections, deep vein thrombosis, and infected pressure ulcers (Volicer et al. 1998). Functional impairment is also an important factor because dependence in feeding and oral care is the most significant factor predicting aspiration pneumonia in institutionalized elders (Langmore et al. 1998).

Avoidance of indwelling urinary catheters is an important factor in preventing urinary tract infections. Antimicrobial prophylaxis may decrease the occurrence of such

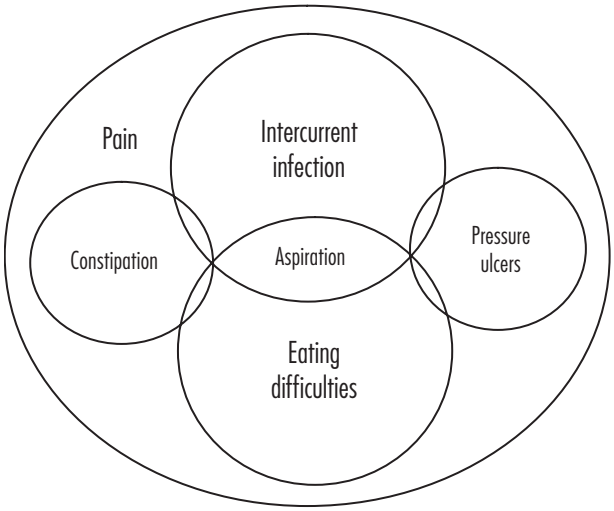

FIGURE 19–2. Secondary conditions in advanced dementia.

infections but often leads to antibiotic resistance. Topical estrogen for atrophic vaginitis decreases the frequency of symptomatic cystitis in elderly women prone to this recurrent disease (Volicer et al. 1998).

Residual urine promotes bacteriuria, whether caused by bladder outlet obstruction, underactive or hyperactive detrusor, or impaired bladder contractility. The residual volume may be reduced by abdominal massage (Crede maneuver) and by straight catheterization on a regular basis. Discontinuation of anticholinergic medications that inhibit bladder contraction can decrease bladder volume. Administration of doxazosin or finasteride may improve bladder emptying in patients with outlet obstruction.

Upper respiratory infections and pneumonia may be reduced by vaccination. Pneumococcal vaccination significantly lowers risk of pneumonia, risk of death from pneumonia, and risk of all deaths (Wagner et al. 2003). This is important because pneumococcal disease is 4.4 times more common in residents of long-term care facilities than in community-living older adults, and pneumococcal strains from long-term care residents are more likely to be antibiotic resistant than strains from community-living adults (Kupronis et al. 2003). The current recommendation is to vaccinate with pneumococcal vaccine all individuals over age 65 years and repeat the vaccine every 5–10 years (Janssens and Krause 2004). Influenza vaccination should be given annually to both residents and staff.

Aspiration

Swallowing difficulty with resulting aspiration is a major risk for developing pneumonia. Aspiration of nasopharyngeal secretions occurs during sleep in half of healthy adults, but the low burden of virulent bacteria in normal saliva together with normal cough reflex and ciliary transport, and normal immune mechanisms protect the airways from infections. Silent aspiration is present in a large percentage of individuals who develop pneumonia (Kikuchi et al. 1994). There may also be choking during food intake. Choking usually starts with thin liquids because swallowing thin liquids requires greater coordination of the muscles of deglutition. Choking can sometimes be prevented by switching from thin liquids to thick liquids (e.g., from milk to yogurt) (Morris and Volicer 2001).

Other strategies to prevent aspiration pneumonia include good oral hygiene, avoidance of smoking and endotracheal intubation, and potentiation of the cough reflex. Periodontal disease and dental plaque are risk factors for development of pneumonia in nursing homes. In residents with teeth, risk factors for development of aspiration pneumonia include requiring help with feeding, chronic obstructive pulmonary disease, diabetes mellitus, number of decayed teeth, number of functional teeth, and presence of specific microbes in the saliva (Terpenning et al. 2001). Oral care decreases incidence of pneumonia, number of febrile days, and death from pneumonia (Yoneyama et al. 2002). Decreased salivary production caused by drugs with anticholinergic effects increases colonization of oral cavity by pathogens (Palmer et al. 2001).

The cough reflex protects against aspiration, and its enhancement decreases the risk of aspiration pneumonia. The cough reflex is improved by angiotensin-converting enzyme inhibitors because they inhibit metabolism of substance P, an important mediator of cough reflex (Sekizawa et al. 1998). Another means to increase cough reflex is dopaminergic potentiation by administration of amantadine (Nakagawa et al. 1999). By contrast, tube feeding actually increases the rate of pneumonia development and pneumonia death rate in residents with evidence of aspiration (Croghan et al. 1994).

Eating Difficulties

Nutritional issues in progressive dementias include apraxia, chewing difficulties, food refusal, and weight loss. Although unable to use utensils, apraxic residents may be still able to feed themselves finger foods. With progression of dementia, late-stage patients will ultimately be unable to feed themselves or drink without assistance. However, adequate nutrition can be provided by hand feeding using a diet adapted to the ability of patients to chew and to their swallowing difficulties. Food refusal may be a symptom of depression and may respond to antidepressant treatment (Volicer et al. 2004). Another medication

that may be useful in dementia-induced anorexia is dronabinol, approved for treatment of anorexia in AIDS (Volicer et al. 1997).

Advanced dementia patients often lose weight. It is always important to determine if the weight loss is caused by staff members' poor feeding practices. Poor professional supervision and inadequate staffing can result in low intake of food and liquids (Kayser-Jones et al. 1999). Target weight for residents with advanced dementia should take into consideration their functional impairment. If they are unable to ambulate, patients experience disuse atrophy of their leg muscles and osteoporosis. In that case, their ideal body weight may be much lower than in conventional weight tables (Khodeir et al. 2000).

Constipation

Constipation is common in institutionalized elders. Up to half of nursing home residents suffer from this condition (Alessi and Henderson 1988), and 58% receive at least one laxative preparation (Lamy and Krug 1978). Constipation may be caused by a combination of decreased enteral neurons (Bassotti et al. 2007), medication side effects, and decreased ambulation. Of the medications used to treat constipation, docusate sodium has very limited effectiveness (Hurdon et al. 2000). Psyllium (McRorie et a. 1998), sorbitol (Volicer et al. 2004), and lactulose or polyethylene glycol (Attar et al. 1999) are more effective.

Enemas are uncomfortable and require more staff time than administration of an oral medication. As the primary goal of care is comfort and preserving dignity, enemas should be avoided. The use of oral laxatives, primarily sorbitol, combined with close monitoring of bowel movements and subsequent changes in dose or frequency as necessary, minimizes the need for use of rectally administered laxatives, which is especially difficult in patients with dementia who become resistive during care (Leonard et al. 2006).

Pressure Ulcers

Pressure ulcers are most commonly located on the sacrum, trochanters, and heels. A recent study of New York nursing homes found that pressure ulcers occurred in 14.7% of nursing home residents with advanced dementia before they died (Mitchell et al. 2004a). On admission from a hospital to nursing home, 10% of residents already had one or more pressure ulcers, whereas only 4.7% of residents admitted from home had pressure ulcers (Baumgarten et al. 2004). Higher prevalence of pressure ulcers was associated with being chairbound or bedridden, being underweight, and fecal incontinence. Several pressure ulcer prevention guidelines have been developed. Adherence to guidelines results in decreased incidence of pressure ulcers in hospitalized critically ill patients (de Laat et al. 2007). However, in nursing homes the adherence to guidelines is relatively low and is characterized by large variations. Pressure ulcers are associated with sepsis, and pressure ulcer–associated death is more common in Alzheimer disease patients than in matched control subjects (Redeling et al. 2005).

Pain

Significant pain is estimated to occur in 26%–83% of elderly nursing home residents (Fries et al. 2002). Frequent sources of pain are osteoarthritis and diabetic neuropathy. Pain in cognitively impaired residents is more frequent and more severe (Leong and Nuo 2007) and is often under treated in cognitively impaired elders because they cannot self-report (Marzinski 1991). Undertreatment is also more common in for-profit facilities (Williams et al. 2005). The importance of pain detection and treatment is recognized in practice guidelines (American Geriatric Society Panel on Chronic Pain in Older Persons 1998). Untreated pain can cause secondary symptoms of sleep disturbance, weight loss, and depression. In persons with advanced dementia, pain can manifest as agitation, increased confusion, and decreased mobility. Untreated pain increases disability and decreases quality of life (Herr and Mobily 1991).

Identifying and measuring pain in persons with advanced dementia is difficult because it is difficult to distinguish between somatic pain and general discomfort in an aphasic individual. Evaluation for possible pain should be initiated when any behavioral changes are observed. Such a change may be oral vocalization, increased resistiveness to care, restless body movements, crying, changes in appetite, withdrawal, rubbing/holding body area, facial grimacing, increased confusion, or a change in sleep. These behavioral changes could be because of unmet physical needs (e.g., being hungry, thirsty, cold), unmet affective needs (e.g., environmental stress, lack of meaningful human interaction), or somatic pain. Serial Trial Intervention showed that meeting physical and affective needs will decrease the behavioral changes in 86% and 76% of individuals, respectively (Kovach et al. 2006). Initiation of nonpharmacological interventions decreased behavioral changes in 62% of remaining individuals, but two-thirds of them required additional treatment with analgesics.

Assessment of pain in cognitively intact individuals or individuals with mild dementia may use a pain scale that can measure pain intensity and location. Because most of these pain scales rely on self-report, individuals with advanced dementia are unable to use even the simplest scales

for pain measurement. Several observational scales for measuring pain in individuals with advanced dementia have been developed and evaluated (Aubin et al. 2007). Use of these scales may help in pain assessment and in communication between health care providers. One of the scales, the Pain Assessment in Advanced Dementia (PAINAD) scale (Warden et al. 2003), is becoming widely used and has been translated into German, Italian, Czech, and Dutch.

Treatment of pain in persons with advanced dementia should include nonpharmacological strategies, such as application of heat or cold, massage, positioning, sensory stimulation, and mild exercise. Pharmacological management should start with administration of acetaminophen. If that is not effective, it is best to proceed to oral morphine and to avoid use of nonsteroidal anti-inflammatory agents because these drugs often cause gastrointestinal side effects that the individual with advanced dementia cannot report. A concentrated solution of morphine can be used even in individuals who have difficulty swallowing because it is absorbed from the oral mucosa. Another option in an individual with chronic pain is administration of fentanyl skin patches. Pain management should strive for pain prevention instead of initiation of treatment after the pain is already present. Thus, chronic pain should be treated with regular doses of analgesics with an option of additional doses if needed.

Seizures and Myoclonus

New-onset seizures are not uncommon in persons with dementias. Onset of seizures in patients with Alzheimer disease was found to occur at the onset of cognitive decline in 3.4% of patients, and 6.8% had a history of seizure disorder and/or were using antiepileptic medications at the time of diagnosis (Lozsadi and Larner 2006). This prevalence increased to 8% in patients followed for 7 years (Amatniek et al. 2006) and to 17% of patients with autopsy-confirmed Alzheimer disease (Mendez et al. 1994). Overall, diagnosis of dementing illness is associated with sixfold increased risk of seizures (Hesdorffer et al. 1996). Seizures are associated with faster deterioration in language ability and increased risk of institutionalization (Volicer et al. 1995). Myoclonus may be even more common, and up to 50% of Alzheimer patients eventually develop myoclonus (Borg 2006). Myoclonus also occurs in 15%–18% of individuals with autopsy-confirmed dementia with Lewy bodies (Borg 2006).

Seizures may be treated after a first episode to decrease the risk of further seizures. Seizures respond well to antiepileptic drugs such as dilantin, carbamazepine, valproic acid, gabapentin, and lamotrigine (Mendez and Lim 2003). However, it should be considered that antiepileptic drugs may have some side effects such as sedation and gait impairment that may increase the risk of falls. Myoclonus requires treatment only if it bothers the individual or interferes with his or her care. Myoclonus is difficult to treat but may respond to gabapentin or tetrabenazine (Kenney et al. 2007).

Behavioral Syndromes of Advanced Dementia

Behavioral syndromes of dementia may be classified as disturbing and nondisturbing (Figure 19–3) (see also Chapter 15 of this volume, "Psychiatric Disorders in People With Dementia"). The nondisturbing syndrome is apathy, whereas the disturbing syndromes are agitation and resistiveness to care. Agitation and resistiveness to care differ in the context in which they occur. Agitation is unprovoked; resistiveness to care is provoked by personal interactions.

Apathy

The prevalence of apathy in cognitively impaired nursing home residents ranges from 17% to 84% (Zuidema et al. 2007), and it is present in all individuals with moderate and severe frontotemporal dementia (Diehl-Schmid et al. 2006). Apathy is associated with severe cognitive deficit, thus, different degrees of dementia severity may explain variation in the reported prevalence. Apathy is often associated with depression; in one study of 150 patients with Alzheimer disease, 12% had apathy plus depression, 7% had apathy alone, and 31% had depression alone (Starkstein et al. 2005). A scale for measuring apathy in demented nursing home residents was recently developed (Lueken et al. 2007).

Apathy has been associated in Alzheimer disease with high neurofibrillary tangle density in the anterior cingulate gyrus (Marshall et al. 2006). Reduced right anterior cingulate perfusion on single photon computed emission tomography (SPECT) is more common in Alzheimer disease patients with apathy (Robert et al. 2006). Apathy scores also are positively correlated with plasma levels of γ-aminobutyric acid (Lanctôt et al. 2007).

Apathy should be addressed even in individuals with advanced dementia because it indicates low quality of life. Even individuals with advanced dementia may experience pleasant events and may interact more with the environment if their apathy is decreased. Nonpharmacological treatment of apathy involves provision of meaningful activities and stimulating environment (Overshott et al.

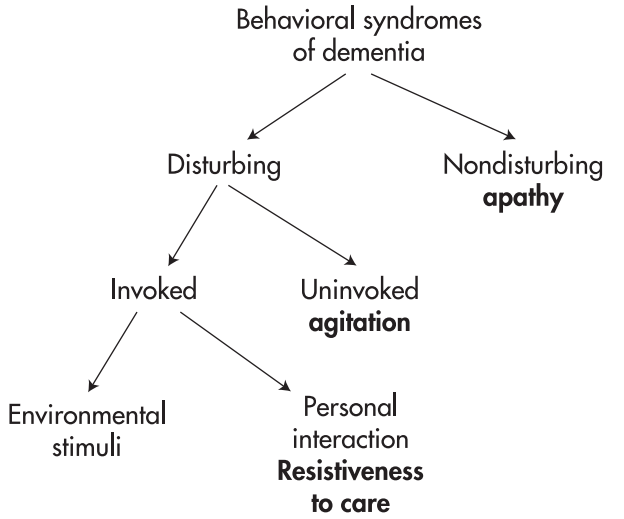

FIGURE 19–3. Behavioral syndromes of dementia.

2004). (The approaches used are described in more detail in the "Personalized Care" section of this chapter.) The pharmacological treatment of apathy lacks data from well-controlled studies. Agents that potentiate dopamine release and/or delay dopamine reuptake in the central nervous system may be most effective. These agents include some atypical antipsychotics and methylphenidate (Roth et al. 2007). Another class of drugs that has beneficial effect on apathy is the cholinesterase inhibitors (Roth et al. 2007).

Agitation

The term *agitation* was used in pioneering research by Cohen-Mansfield (1988) to describe the disturbing behavioral symptoms of dementia. Factor analysis of the Cohen-Mansfield Agitation Inventory yielded three factors: aggressive behavior, physically nonaggresive behavior, and verbally agitated behavior (Cohen-Mansfield et al. 1989), but these three categories of agitation do not take into consideration the context in which behavior occurs. Context is important because the same behavior can have different meanings in different contexts and require different management. For instance, negative vocalization by an individual not engaged in any activity may express an unmet need or psychological distress, whereas negative vocalization during assistance with an activity of daily living may indicate lack of communication between the individual and staff member. The approach for management of this behavior is also different: evaluation and satisfaction of unmet needs in the first case and better communication or procedure modification in the second.

Labeling a behavior "aggressive" suggests that the behavior is intrinsic to the individual with dementia. In most cases, however, individuals with dementia initiate aggressive behavior only with provocation. Aggressive behavior is most often directed at staff in the context of personal care (Bridges-Parlet et al. 1994). In most cases, aggression is preceded by verbal outbursts and resistance to caregiving. This "resistiveness to care" is often caused by patient's belief (often delusional) that the care is not needed. Therefore, the patient defends against the caregiver and, if the caregiver persists in efforts to provide care, the patient may become combative. However, in that situation it is a mistake to label the patient aggressive because it shifts the blame from the caregiver who is using an inappropriate approach or is insufficiently communicating to the individual with dementia.

For these reasons, it is useful to differentiate between agitation and resistiveness to care. Use of the term *agitation* should be limited to a situation outside of caregiving activities. *Agitation* is better defined as behaviors that communicate to others that the person with dementia is experiencing an unpleasant state of excitement, are observable without subjective interpretation, are not provoked by caregiving activities, are unrelated to known physical needs of the patient that can be remedied, and are without known intent (Hurley et al. 1999). Before labeling any behavior as agitation, physical and environmental causes of the behavior should be eliminated. These causes include untreated pain, hunger, thirst, inappropriate environmental temperature, noise, and so on. Agitation should be treated according to the primary consequence(s) of dementia that is/are responsible and can be measured by direct observation.

Resistiveness to Care

Resistiveness to care comprises the various behaviors with which persons with dementia withstand or oppose the efforts of caregivers and can be measured by a direct observation during care (Mahoney et al. 1999). Separation of agitation from resistiveness to care is supported by different relationships of these syndromes to severity of dementia. Analysis of Minimum Data Set data from 23,837 residents with dementia showed that although agitation occurs even in mild dementia and that prevalence does not vary with dementia severity, prevalence of resistiveness to care increases with dementia severity and is most common in patients with very severe cognitive impairment (Volicer et al. 2007) (Figure 19–4). This study also showed that prevalence of resistiveness to care increases with decreased ability to understand spoken language and that most residents who were rated as abusive were also resistive to care.

Several factors increase probability of resistive behavior. Delusions and hallucinations may prevent recognition

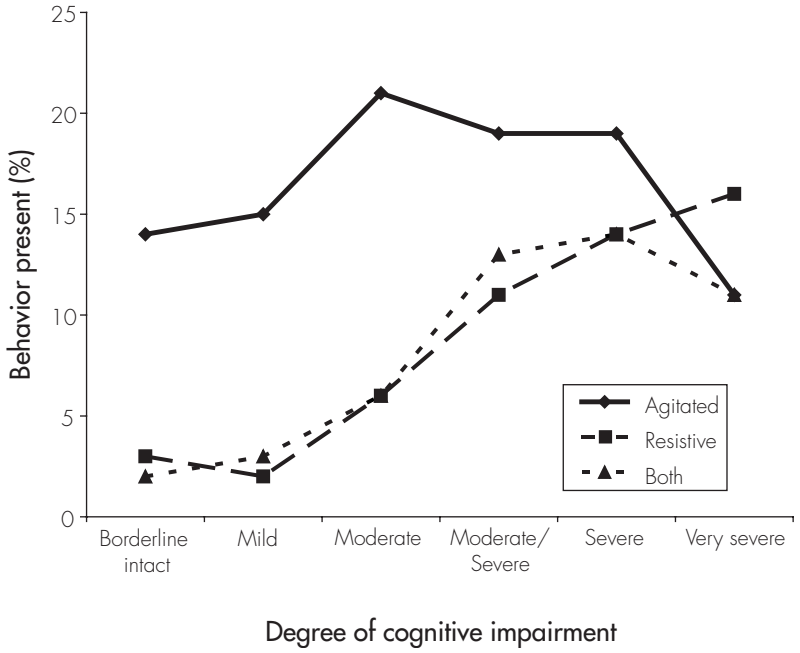

FIGURE 19–4. Prevalence of agitation and resistiveness to care in VA nursing home residents with different severities of cognitive impairment.
Source. From Volicer L, Bass EA, Luther SL: "Agitation and Resistiveness to Care Are Two Separate Behavioral Syndromes of Dementia." *Journal of the American Medical Directors Association* 8:527–532, 2007.

of the need for care or lead to misidentification of staff persons. Depression often increases resistiveness to care. Management of these factors may decrease resistiveness to care, but the most important factor is caregiver approach. Therefore, caregiver behavior should always be evaluated when resistiveness of care occurs before initiation of any pharmacological therapy. The goal of care is to prevent escalation of resistive behavior to combative behavior.

The approach used by the caregiver is crucial. Relaxed and smiling caregiving helps calm the individual with dementia. It is important to avoid making demands that create stress or are beyond the ability of the individual with dementia, rushing through help with activities of daily living, touching without warning, painful procedures, and overstimulation. It is helpful if the caregiver stays within the field of view, provides visual and verbal preparation for maneuvers that may seem intrusive to the individual, and provides physical support and touch to guide the desired motor acts in apraxic individuals. It is also important to express respect for the individual with dementia by allowing the person to maintain some control. Distraction also may be used to direct the individual's attention away from the stressful stimulus. Engaging an individual in conversation on a favorite topic or reminiscing about happy memories takes the focus away from the task and places it on the person. This person-centered approach is effective even with individuals who have significant cognitive and language impairment. In an institutional setting, distraction may be accomplished by using two caregivers. While one caregiver engages the individual's attention by talking or singing, a second caregiver performs the needed care.

Another important factor is the care environment. This is especially important for bathing. The bathroom should feel private and personal, it should be warm, and should have relaxing music, soft light, low noise level, homelike furnishings, and aromas to evoke positive memories, and the bathing equipment should be comfortable and functional. Some individuals prefer to bathe in the morning and some in the afternoon or evening. Replacing showers or tub baths with bed baths is much less stressful for some individuals with dementia (Sloane et al. 1995).

Pharmacological management should take into account the possible causes of resistiveness to care. The possibility that resistiveness is caused by pain experienced during care procedures should be considered, and, if painful, premedication with analgesics before a care episode should be instituted. If depression is present, antidepressant treatment often decreases the resistive behavior. Delusions are a common cause of resistive behavior, and if the behavior cannot be managed by behavioral strategies, antipsychotic therapy may be useful.

Depression

The diagnosis of depression in advanced dementia is difficult because it cannot rely on verbal examination. However, depression is quite common in earlier stages of dementia (Thompson et al. 2007), and because it is probably caused in part by destruction of the serotoninergic system, it is improbable that it would not be present in advanced dementia. It is important to consider vegetative symptoms such as anorexia, sleeping difficulties, and psychomotor agitation/retardation as possible symptoms of depression. Some patients exhibit mood swings. Depression may lead to agitation, food refusal, and repetitive vocalization. Depression may also aggravate resistiveness to care because depressed individuals tend to ignore activities of daily living. Depression increases the propensity for escalation of resistiveness to combativeness, and it was significantly more common among residents with dementia who manifested physical or verbal aggression than in those without such behaviors (Menon et al. 2001). Depressive symptoms may be improved by providing sufficient meaningful activities but often require treatment with antidepressants.

Even though the formal diagnosis of depression may not be possible in individuals with advanced dementia, they may benefit from antidepressant treatment. The first-line drugs for treatment of depression in individuals with dementia are selective serotonin reuptake inhibitors (SSRIs) (see also Chapter 15, "Psychiatric Disorders in People With Dementia," and Chapter 16, "Pharmacological Treatment of Neuropsychiatric Symptoms," of this volume). Sertraline was found not only to improve mood in individuals with advanced dementia but also to decrease their anorexia (Volicer et al. 1994b). Venlafaxine or bupropion may be used in persons who do not tolerate SSRIs. Another option is mirtazepine, which may also stimulate appetite. Trazodone is relatively ineffective as an antidepressant but is useful for treatment of insomnia.

Caregivers

Functional dependence, unsafe behavior, and behavioral symptoms of dementia create a need for constant patient supervision that poses a great burden for the caregivers (see also Chapter 20 of this book). Caregivers often have to cope with functional impairment and behavioral symptoms for many years. Caregiving in dementia is more stressful than caregiving for physically impaired older adults; caregivers of individuals with dementia give up their vacation or hobbies more often, have less time for other family members, and report more work-related difficulties than caregivers of individuals with physical impairment (Ory et al. 1999).

Although caregiver distress is related to the direct provision of care for the demented individual, the distress does not cease after the individual is institutionalized. Caregivers often feel that they have failed their loved ones by placing them in an institution. Social support for caregivers of institutionalized individuals with dementia is very important because depressive symptoms and anxiety is as high in caregivers after they institutionalized their relative as when they were in-home caregivers. The use of antidepressants does not change and the use of anxiolytics increases in caregivers after placement (Schulz et al. 2004). Caregivers of individuals with dementia involved in a hospice program continue being at risk for depression and having lower life satisfaction and physical health than noncaregivers (Haley et al. 2001).

Despite the long course of progressive dementias, one-quarter of caregivers are not prepared for their relative's death (Hebert et al. 2006). These caregivers had more depression, anxiety, and complicated grief symptoms than caregivers who reported that they were prepared for death of their relative. Bereavement support is very important for caregivers of individuals with dementia because almost half of them develop depression after patient's death, and a significant degree of depression was also found almost 2 years after the death of the care recipient (Bodner and Kiecolt-Glaser 1994). Complicated grief developed in 20% of caregivers after the death of their care recipient. Complicated grief was more likely to develop if the caregivers had preloss depressive symptoms, had a positive experience with caregiving, and were caring for a more cognitively impaired person (Schulz et al. 2006). Frequent attendance of religious services was associated with less depression and complicated grief (Hebert et al. 2007). It is very important to monitor physical and mental status of caregivers during a patient's life but also after the patient's death and provide treatment for depression if necessary.

Decisions About End-of-Life Care

Individuals with advanced dementia cannot make decisions about their end-of-life care, and therefore these decisions have to be made by their surrogates. The decisions can be made on the basis of the person's previous wishes,

or, when these wishes are not known, on the basis of the person's best interest as perceived by the surrogate (see also Chapter 22). The resident's wishes may be formalized in a living will that was completed when the person still had testamentary capacity or may be in the form of verbal communication expressing the person's philosophy regarding end-of-life care. Living wills are often too general and may not cover advanced dementia. An opportunity for formulating advance directives is mandated at the time of admission to a nursing home. However, this discussion is often focused primarily on preference regarding cardiopulmonary resuscitation and reviewed only after the crisis of acute illness and hospitalization.

Management of medical issues in advanced dementia should be based on well-defined goals of care that avoid treatments that may provide little benefit but cause significant discomfort. The goals of care should be formulated well in advance to avoid making decisions in a crisis situation.

The three goals of medical care are prolongation of life, maintenance of function, and comfort (Gillick et al. 1999). Ideally, all these goals should be met simultaneously. However, this is not always possible because aggressive medical interventions, such as transfer to an acute care setting, may prolong life but result in decreased function and inflict significant discomfort. Decisions about medical care should keep in mind not only the goals of care but also the evidence for beneficial and detrimental effects of various medical interventions.

Decisions about care for a relative with dementia have several dimensions (Figure 19–5). The involvement of the treatment team is very important in collaborative decision making. Family members often feel that involvement of health care professionals in end-of-life care is often insufficient and creates an extra burden on dying nursing home residents and their families (Shield et al. 2005). More than 15 minutes of discussion of advance directives was associated with greater satisfaction with care for health care proxies (Engel et al. 2006). Unfortunately, physicians are often more conservative than patients' relatives in avoiding aggressive medical interventions when caring for individuals with advanced dementia (Rurup et al. 2006). For instance, often they would not want a feeding tube for themselves if they suffered from advanced dementia, but they favor tube feeding for their patients. Attitudes of family members differ according to the setting of care. In rural settings, relatives are more accepting of death and hope it will be quick and peaceful, whereas relatives in urban settings have a wider range of attitudes toward death, from unambiguous acceptance of immediate death to all-out efforts to prevent death (Gessert et al. 2006); this may account for the lower use of feeding tubes and less extended hospitalizations and intensive care unit (ICU) admissions in residents of rural nursing homes (Gessert et al. 2006b).

Cardiopulmonary Resuscitation

The immediate survival of resuscitated nursing home residents is 18.5%, with only 3.4% discharged from the hospital alive (Finucane and Harper 1999). Because presence of dementia reduces the probability that cardiopulmonary resuscitation (CPR) will be successful by a factor of three (Ebell et al. 1998), only 1% of demented residents suffering cardiac arrest can be expected to be discharged alive from the hospital. Even this potential benefit may be outweighed in persons with severe dementia. CPR is stressful for those who survive because they may experience injuries such as broken ribs and often require a respirator. The ICU environment is not conducive to care for individuals who are confused, and they often develop delirium. In addition, patients who are discharged alive from the hospital after CPR are much more impaired than they were before the arrest (Applebaum et al. 1990).

Transfer to Acute Care Setting

Transfer of demented individuals to an emergency room or hospital exposes them to serious risks. Even cognitively intact hospitalized elders experience confusion, falls, poor food intake, and incontinence (Covinsky et al. 2003). These symptoms are often managed by medical means such as psychotropic medications, restraints, nasogastric tubes, and indwelling catheters, which expose the patient to complications including thrombophlebitis, pulmonary embolus, aspiration pneumonia, urinary tract infection, and septic shock. Hospitalized individuals with dementia often are exposed to aggressive medical interventions that increase their discomfort. Measurement of arterial blood gases and use of urinary catheters is more common prior to death in patients with dementia than in patients without dementia, whereas referral to palliative care and use of palliative medications is less common (Sampson et al. 2006).

Transfer of long-term care facility residents to an emergency room or hospital for treatment of infections and other conditions may not be optimal for managing these problems. Pneumonia survival is actually better in residents treated in a nursing home; the 6-week mortality rate was 18.7% in nonhospitalized residents and 39.5% in hospitalized residents in one study (Thompson et al. 1999). Similarly, a larger proportion of hospitalized individuals had worsening of their functional status or died at 2 months after the episode of pneumonia than individuals

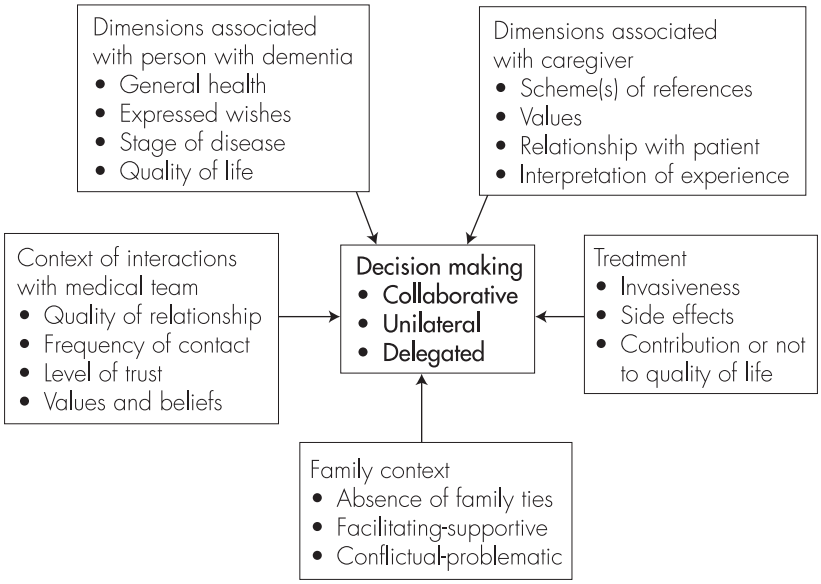

FIGURE 19–5. Dimensions associated with decision making at the end of life of a relative with dementia.
Source. Adapted from Caron et al. 2005.

treated in the nursing home (Fried et al. 1997). Thus, the available data indicate that transfer to an emergency room or hospital has significant risks and relatively few benefits for individuals with severe dementia. Therefore, this strategy should be used only when consistent with overall goals of care and not as a default option.

There is some evidence that end-of-life care is better when provided in a private residence than in a nursing facility. Individuals with dementia who died at home had less pain and shortness of breath and more palliative care than individuals with dementia dying in a nursing home (Mitchell et al. 2004a). Hospice care, pain control, and psychiatric treatment of behavioral symptoms allow individuals with dementia to stay at home longer before dying (Volicer et al. 2003).

Tube Feeding

There is no evidence that long-term tube feeding is beneficial in individuals with advanced dementia. Tube feeding does not prevent aspiration pneumonia and actually might increase its incidence because it does not prevent aspiration of nasopharyngeal secretions and of regurgitated gastric contents (Finucane et al. 1999). Nasogastric tubes may cause infections of sinuses and middle ear, and gastrostomy tubes may cause cellulitis, abscesses, and even necrotizing fasciitis and myositis. Contaminated feeding solution may cause gastrointestinal symptoms and bacteriuria. Tube feeding does not prevent malnutrition, and it does not increase survival in individuals with progressive degenerative dementia. Use of a nasogastric tube actually may cause death from arrhythmia during insertion and from perioperative mortality in percutaneous endoscopic gastrostomy tube placement. Occurrence of pressure ulcers is not decreased by tube feeding, and it may be actually increased because of the use of restraints and increased production of urine and stool. There is also no evidence that tube feeding promotes healing of pressure ulcers or improves functional status of individuals with severe dementia (Gillick 2000). Forgoing artificial nutrition and hydration in patients with severe dementia who no longer eat or drink is not associated with high levels of discomfort because individuals who are dying no longer feel hunger or thirst (Pasman et al. 2005).

In addition to the lack of benefits, tube feeding has many adverse effects including discomfort caused by both the tube and by the restraints that are often necessary to prevent tube removal. Tube feeding also deprives the patient of the taste of food and contact with the caregivers during the feeding process. This imbalance of burdens and benefits of tube feeding justifies the recommendation that tube feeding should not be used in individuals with advanced dementia.

Antibiotic Therapy

Antibiotic therapy is quite effective for an isolated episode of pneumonia or other systemic infection. In most patients, it is possible to limit antibiotic therapy to oral preparations. It is preferable to avoid intravenous therapy in

individuals with severe dementia because of the associated need for restraint. In patients with poor oral intake, intramuscular antibiotics can be used.

The effectiveness of antibiotic therapy is limited by the recurrent nature of infections in advanced dementia. Antibiotic therapy does not prolong survival in cognitive impaired patients who are unable to ambulate and who are mute (Fabiszewski et al. 1990). Antibiotics also are not necessary for maintaining comfort in demented individuals who can be maintained equally well with analgesics, antipyretics, and oxygen if necessary (van der Steen et al. 2002). In addition, antibiotic use may have adverse effects, including gastrointestinal upset, diarrhea, allergic reactions, hyperkalemia, and agranulocytosis. Diagnostic procedures such as blood drawing and sputum suctioning that are necessary for rational use of antibiotics cause discomfort and confusion in demented individuals. Use of antibiotics in patients with advanced dementia should, therefore, take into consideration the recurrent nature of infections and other factors that significantly reduce benefits of antibiotic treatment.

Hospice Care

The use of hospice for individuals with a primary diagnosis of dementia is increasing, but only 6% of nursing home residents with advanced dementia are referred to hospice (Mitchell et al. 2004b). The main barrier to more widespread use of hospice care for residents with advanced dementia is the Medicare requirement that a patient have a prognosis of death within 6 months. Two methods for estimation of prognosis based on the Minimum Data Set evaluations have been developed (Mitchell et al. 2004c; Wallace and Prevost 2006), but there is no clear cutoff point that can be used to eliminate hospice services for residents with advanced dementia who will live longer than 6 months without excluding many residents who die within 6 months.

Nursing home physicians are more than 90% accurate in their prognosis for terminally ill noncancer patients when death occurs within 7 days, but for a longer period of time their predictions become inaccurate (8–21 days, 16%; 22–42 days, 13%) and are overly optimistic (Brandt et al. 2006b). Thus, it is almost impossible to predict with any certainty which individuals with advanced dementia will die within 6 months.

Applying strict criteria for hospice eligibility may be counterproductive because most studies show that Medicare costs are lower for residents enrolled in hospice care than for nonhospice residents (Miller et al. 2004). Hospices provide important services both to the resident and family. Pain management is improved by documentation of pain assessment, and hospice residents are also more likely to be free of psychiatric symptoms (restlessness, sleep problems, agitation, nervousness, aggression) than residents without hospice care (Bekelman et al. 2005). Hospice services are also important for the family members and caregivers of persons with dementia. Caregivers value the continuous involvement of the patient's primary physician in his or her care and an emphasis on avoiding hospitalization (Casarett et al. 2002). Hospices also provide social support and bereavement services that are not available in nursing homes (Murphy et al. 1997).

Quality of Life

People with late-stage dementia continue to have psychosocial needs. By the late stage the person often lives in a long-term care facility in which the staff finds it easier to provide medical treatment and personal care than meaningful activities for persons with limited communication skills. Long-term care staff members are trained to perform activities of daily living such as feeding, dressing, and grooming. Depending on the shift, nursing assistants may have more than 10 residents for whom to care. Personal care becomes impersonal care. Activity professionals in nursing facilities are also challenged to provide meaningful activities to residents who have a short attention span, sleep through activity programs, and are unable to communicate. Residents in long-term care facilities who are unable to participate in activity programs are left alone in their rooms or "parked" by the nurses' station. Some residents are taken to an activity in which they spend the majority of time asleep. Other late-stage residents become agitated from overstimulation by an activity they cannot comprehend. When a resident does not attend activities, activity professionals provide individual room visits. These visits may be offered several times a week, but they are usually brief so that residents with advanced dementia are isolated.

Families often decrease the number and duration of their visits as they prepare for the death and acknowledge that the person they love is unable to recognize them or communicate in a meaningful way. This further isolates the person with advanced dementia. Families are admonished not to resuscitate, hospitalize, treat infections, or tube feed, but they are not offered suggestions to help the person with dementia to experience quality of life. However, it is possible to provide individualized care that promotes quality of life even to individuals with advanced dementia, as will be explained in the following section.

Personalized Care

We believe that personalized care is an important element in maintaining quality of life for persons with advanced dementia. To this end, we have developed a program we call Namaste Care (Simard 2007). *Namaste* is a Hindu term meaning "to honor the spirit within." The program offers residents gentle touch, a pleasant environment, meaningful activities, music, and aroma therapy (Nguyen and Paton 2008). It is a person-centered approach, recognizing and treating each person as an individual and is offered in a group setting to reduce isolation. It enhances the care provided by nursing home staff members and helps family members feel that something positive can still be done for their loved ones.

Namaste Care does not require additional staff or expensive supplies or equipment and is easy to implement. When at least eight residents are in the Namaste room, one nursing assistant's assignment is to be the Namaste carer. The Namaste carer who is assigned to the Namaste Room may have a lighter assignment and would not have a resident who needs a bath that day. The nursing assistants not assigned to the program are responsible for monitoring the needs of the Namaste carer's residents who are not in the program.

In this program, both family and nursing home caregivers offer special and individualized meaningful activities to the person with advanced dementia. When implemented, staff members and families frequently see changes in residents who previously had shown little response to environment. Residents with advanced dementia may simply make eye contact, smile, have less agitated behavior, or make sounds indicating pleasure. Namaste Care enables staff members and families to see that they have a way to help the person with advanced dementia to enjoy life.

A Namaste Care room should have a sink, windows to allow natural light, and a way to close it off to limit noises that would disturb the program. Attempts are made to create a homelike atmosphere, including plants, pictures, and curtains.

Each day in Namaste Care begins with the residents being assisted with breakfast, groomed for the day, and taken to the Namaste Room. This room has been prepared with soothing music, dimmed lights, and the scent of lavender, which has been found to decrease agitation in individuals with dementia (Lin et al. 2007). The resident is greeted by name and touched. The individual may be greeted by first name, nickname, or title, depending on the individual's preference.

For most late-stage dementia patients, a wheelchair is not comfortable; they are often slumped in the chair as they sleep for most of the day. In Namaste Care, after residents are greeted they are placed in comfortable lounge chairs and quilts are tucked around them. If they are not at risk for choking, residents are offered a small lollypop. Sucking a lollypop seems to be pleasing and helps to keep their mouths moist. When the majority of the residents are in the room, programming commences.

Each resident has a plastic bag containing a comb, brush, fingernail clippers, and other personal items such as lipstick or a favorite aftershave lotion. The Namaste carer gently washes each person's face and brushes his or her hair. This grooming activity is accomplished as a process of gentle loving care. The residents are spoken to about their lives or about the day, as if it were normal conversation. They are also offered a beverage (juice, water, smoothies, and other high-caloric beverages) to help maintain hydration, often a difficult task at this stage of their illness.

Sights, sounds, and scents of the morning may be introduced, using small stuffed birds and real bird sounds. A bouquet of lilacs taken to each individual may be used as a sign of spring, and grass cuttings may simulate the scent of summer (some men may push the bag of grass away because they remember having had to cut grass). At the end of the morning, nursing assistants come back to the Namaste Room. Each resident is thanked for having been present and invited to return after lunch.

When lunch and grooming are completed, some residents are taken back to their rooms for a rest, and others return to the Namaste Room. The procedure is the same as in the morning with each resident welcomed and placed in a comfortable chair. Because there are fewer residents in the afternoon, the Namaste carer can soak feet and wash and lubricate feet and legs. Range of motion exercises are accompanied by music. Families visit in the afternoon. Because they often do not know what to do with their loved ones, the Namaste carer offers suggestions. They may be encouraged to massage residents' hands and arms or feed them ice cream if choking is not a concern. Family members may also enjoy conversing with the Namaste carer because many spouses are very isolated when their loved ones are in a nursing facility.

Programs may offer a video of some nature scenes such as a rain forest, reading of special poems, or favorite spiritual or religious offerings. Small items such as wind chimes and singing bowls often receive smiles from patients. The Namaste carer knows elements from the life story of each resident and plans activities or interactions that can be meaningful to him or her. Beverages and high calorie foods, such as ice cream, puddings, shakes, and juices, are offered in the afternoon to combat weight loss.

At the end of the day, each resident is again thanked for attending and invited back the next day. The room is cleaned and stocked for the next day. Where Namaste Care has been implemented, residents, their families, and staff are grateful that they have some meaningful activity to offer residents in the advanced stage of dementing illness.

Residents are also honored as individuals through the dying process. All attempts are made to have someone present for the dying resident if the family is not available. After death, the residents remain in the Namaste Care program until they leave the nursing facility. The body is prepared and funeral home notified. When attendants arrive to take the body to the funeral home, the body is draped with a flag if the resident was a veteran or draped with a homemade quilt if they have not served in the military. The body is then taken to the hearse with staff and family walking alongside the gurney as staff offer their last farewell to the person they have honored in life and now in death.

Several days after the death, staff members meet to discuss the death. They review pain and symptom management. The meeting ends with remembrances of the resident, and they are thanked for helping the resident maintain quality of life. A sympathy card is distributed for each staff member to sign.

KEY POINTS

- Provide personalized care.
- Avoid painful treatments and procedures.
- Provide adequate pain relief.
- Avoid tube feeding and chronic catheterization.
- Treat chronic conditions such as hypertension and diabetes conservatively.
- Long-term interventions such as a low-cholesterol diet are not appropriate.
- Avoid transfer to emergency or hospital facilities when possible.

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PART V

Caregiving, Legal, and Ethical Issues

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CHAPTER 20

Supporting Family Caregivers

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Introduction

It is currently estimated that 8.9 million caregivers (20% of all adult caregivers) care for someone with dementia who is age 50 years or older (Family Caregiver Alliance 2007). Caregivers provide 8.5 billion hours of care, valued at almost $83 billion (Alzheimer's Association 2007). As the general population ages, the number of people in need of care will continue to increase. Caregivers of persons with Alzheimer disease and other dementias shoulder a particularly heavy burden. The task of caring for someone with dementia is one of great challenge, changing over time (Perren et al. 2006), often at the expense of caregivers' well-being (Schulz and Martire 2004). The type of care provided by dementia caregivers is more physically and emotionally demanding, more time-consuming, and takes a heavier toll on work and family life than that of other caregivers (Ory et al. 1999). However, dementia caregivers often do not receive the help and support they need (Alzheimer's Association 2004).

Who Are the Family Caregivers?

There are numerous definitions of "informal caregiver." The consensus is that informal caregivers are family members, friends, and neighbors who provide care that exceeds the normal amount of care provided within such relationships. The care provided may be primary or secondary, full- or part-time, and the caregiver may reside with the care recipient or separately. The care services provided are often in the form of bathing, dressing, toileting, feeding, and/or other personal and household management activities (Schulz and Martire 2004; Thompson et al. 2006). Formal caregivers, by contrast, are paid professionals such as home health aides, visiting nurses, and nursing staff of long-term care facilities. The focus in this chapter is on informal family caregivers.

The model dementia family caregiver is a married woman age 50 to 64 years, with a high school education or less, who is employed full-time outside the home (Alzheimer's Association 2004). However, there has been an increase in the number of male caregivers, who now comprise 43% of dementia patient nonpaid caregivers. Although

a general description of dementia caregivers offers a broad sense of who caregivers are, numerous differences emerge when caregiving is examined in a cultural context (Dilworth-Anderson et al. 2004).

Among non-Hispanic whites, informal caregivers are predominantly female spouses of dementia patients who are dealing with their own age-related decline as well. Non-Hispanic white caregivers tend to have higher levels of education and financial resources than their ethnic minority counterparts (Coon et al. 2004).

In the Hispanic population, caregiving is usually provided by the adult children of the dementia patient, most often the daughters. Relying on outside support is considered "shirking one's responsibilities" and unnecessarily burdening outsiders (Montoro-Rodriguez et al. 2006).

Among African Americans, caregiving duties are often shared among a number of family members and "fictive kin" (nonblood relatives who are regarded and treated as family) rather than a single caregiver. These caregivers are more likely to be unmarried adult children of the care recipient, with less formal education and financial resources than white caregivers.

Among most Asian Americans, dementia caregiving is typically the responsibility of the firstborn son and his wife, or an adult daughter, if there is no son. Filial piety, or sense of duty to one's elders, is such an important value among Asian Americans that caregivers may forego their own health and well-being in service of their parents' care (Gallagher-Thompson et al. 2003c).

In all cases, added strain may exist for caregivers who are also caring for their own children. Although these social and ethnic categories are used by the U.S. Census and are useful in the service of research, much heterogeneity exists within each ethnic group. More detailed information on this subject is provided in *Ethnicity and the Dementias*, edited by Yeo and Gallagher-Thompson (2006).

Ethnic Variation in Knowledge of Dementia

Due to difficulties in parsing out cognitive changes that might be due to normal aging and those attributable to early-stage dementia, many individuals do not seek medical professional help until the changes have become relatively severe. Additionally, cultural factors play a role in how aging and dementia are viewed, as knowledge of dementia varies across ethnic groups (Ayalon and Arean 2004). In examining such cultural differences, Gray and colleagues (in press) found that white caregivers were more knowledgeable of Alzheimer disease and its medical treatment than the Hispanic and Chinese American caregivers with whom they were compared. Additionally, Hispanic and Chinese Americans were more likely to attribute dementia to normal aging than whites. Furthermore, the minority groups tended to believe that Alzheimer disease is diagnosable by a blood test, whereas their white counterparts did not. Such variation in understanding of dementia may hinder families' ability to seek services and medical attention for their loved ones. For some families struggling with a loved one's memory problems, the diagnosis of a medical condition can be a relief, providing an explanation of otherwise puzzling behaviors. However, that initial sense of relief may wear off as families face the challenging road ahead. In some families, the changes in cognitive functioning and behavior that accompany a dementia syndrome may be attributed to culturally bound syndromes such as "spells" and "worriation" among African Americans (Coon et al. 2003) and mental illness among Hispanic/Latinos. "Spells" are episodes of altered consciousness that include extreme anger or irritability, fugue states, trances, or walking visions (i.e., hallucinating a deceased relative) (Hargrave 2006). "Worriation" is described as a combination of anxiety and perseverative thinking that can cause brain damage (Hargrave 2006). In addition, individuals from African American cultures may place greater importance on social and role functions rather than cognitive function; concern may be raised in the event that social or role functions are not fulfilled rather than about impaired cognitive function, which can delay diagnosis and treatment.

Within the Latino/Hispanic community, dementia is not widely understood. It is usually viewed with stigma as a mental state that can be controlled. As such, Latino/Hispanic families often hide the problems associated with dementing illness due to shame and embarrassment, resulting in less use of external support (Coon et al. 2004; Yeo and Gallagher-Thompson 2006).

It is important to consider the varying levels of understanding of dementia within a cultural context, so that caregivers and care recipients can be provided with culturally appropriate disease education.

Caregiving Through the Stages

Although there can be general expectation about the progression of disease, no one can predict the future for an individual. This uncertainty is stressful in and of itself. Early on, caregivers and care recipients are likely to spend time adjusting to the new diagnosis and beginning to obtain information about the disease. At this time, caregiving is confined to helping with instrumental activities of daily living such as finances. Later, caregiving shifts to a more full-time role, with safety of the care recipient a priority. During this time, both caregivers and care recipients will need support, given that behavioral problems often grow. Finally, professional support may be needed, as the care-

giving tasks increase and become more physically and emotionally taxing; at this time caregivers may implement nursing home placement.

Caregiver Psychological and Physical Health

Caregivers of dementia patients are at increased risk for physical and psychiatric illness (Connell et al. 2001; Pinquart and Sorensen 2003; Schulz and Martire 2004). The literature examining the relationship between caregiving and health effects is extensive (Schulz and Martire 2004; Vitaliano et al. 2003), but the data do not show a consistent relationship between objective burden and physical well-being. Some caregivers report greater well-being despite increased levels of objective burden. In an effort to explain the variation in individual responses to stressors, Folkman and Lazarus (1986) developed a model in which stress is subjective—the outcome of an individual's appraisal of a particular situation.

Model of Stress and Coping

Folkman and Lazarus's stress and coping model theorizes that appraisal of one's resources and ability to cope modifies one's perceived level of stress. Caregivers who perceive low levels of support and ability to carry out their caregiving tasks, regardless of the care recipient's level of impairment, experience greater levels of distress than those who perceive those same resources more positively. This model is useful for understanding cultural differences in response to caregiving stressors.

Psychological Well-Being

Caregivers of individuals with dementia experience significantly higher levels of psychological morbidity, depression, anxiety, stress, loneliness, and burden than their noncaregiving counterparts (Schulz and Martire 2004). Pinquart and Sorensen (2007) found perceived burden and depression were more related to poorer caregiver health than objective measures of stress. However, ethnic variations regarding the impact of stress have been reported (Sorensen and Pinquart 2005). Caregiving tasks are reported to be greater among African American and Asian caregivers than among white caregivers (Pinquart and Sorensen 2005). Even though African American caregivers reported greater physical and cognitive impairment regarding their care recipients, they did not report increased behavior problems. This finding indicates the subjective nature of caregiving and its relation to perceived burden, given that African American caregivers report the lowest levels of depression and Asians and Hispanics the highest levels (Pinquart and Sorensen 2005). The tendency of Latinos/Hispanics to treat their care recipients within their own community and to avoid seeking outside resources or sharing information about family members may create a greater burden (Coon et al. 2004) and result in higher rates of depression and more severe symptoms among the caregivers in this group than in other minority groups (Sorensen and Pinquart 2005). Risk factors for caregiver depression, regardless of race, include female spousal status, greater care-recipient memory impairment, and behavior problems (Pinquart and Sorensen 2003, 2005, 2007).

Physical Well-Being

As physical and emotional demands of caregiving increase, family caregivers are at greater risk of damage to their physical health (Pinquart and Sorensen 2007). Evidence is accumulating not only to support caregivers' subjective complaints of poor health but also to document physiological changes in association with dementia caregiving. For example, women caregivers (compared with a comparable sample of noncaregivers) have significant dysregulation in diurnal cortisol levels, with failure to subside after the normal morning peak (Gallagher-Thompson et al. 2006). There also appears to be earlier onset of cardiovascular disease (Mausbach et al. 2007) and increased risk of mortality among stressed spousal caregivers that could not be accounted for by age and health status (Schulz and Beach 1999). Spousal caregivers may be particularly exposed to numerous long-term stressors as care recipients' health declines (Vitaliano et al. 2003). Depressed caregivers also appear to be at greater risk for developing physical health problems (Mahoney et al. 2005). In addition, at least one study has revealed that Latino caregivers rated their physical health as significantly worse than white counterparts, and showed poorer health habits—such as regularly eating fewer than two meals a day (Rabinowitz and Gallagher-Thompson 2007).

In a meta-analysis, Pinquart and Sorensen (2007) examined the role of sociodemographic variables, caregiving stressors, caregiver resources, and psychological distress of the caregiver on the physical health of informal caregivers. Among the caregiver stressors, behavior problems of care recipients had the strongest association with caregiver health, burden, and depression, but less for physical health outcomes. Caregivers with greater financial resources who did not co-reside with the dementia patient reported better physical health. Although younger caregivers reported better physical health, they tended to report higher levels of burden and depression. However,

cultural differences should be taken into consideration regarding this finding, considering that caregivers of nondominant cultures may present differently. Latino caregivers of individuals with dementia report lower appraisals of stress, greater perceived benefits of caregiving, and more use of religious coping than white caregivers (Coon et al. 2004). Within-group variation also occurred, and was related to varying levels of Latino acculturation (Shurgot and Knight 2004). Additionally, objective measures of stress and depression vary among different ethnic groups. Cortisol dysregulation was significantly greater among Latino caregivers than demographically comparable white women (Gallagher-Thompson et al. 2006).

In a study examining risk factors and health status of male caregivers, Shanks-McElroy and Strobino (2001) found that increased levels of care provision, high levels of perceived stress relating to care recipient behavior, greater amounts of problem behavior, and low satisfaction with leisure activities were risk factors for poor caregiver health. Nonspousal younger caregivers of dementia patients reported higher rates of depression and perceived burden than other caregivers (Pinquart and Sorensen 2005); however, cultural and gender differences were conveyed. A study by Atienza et al. (2001) found that even though male and female spousal caregivers both demonstrated increased blood pressure when discussing caregiving difficulties, female caregivers had greater increases than male caregivers. Additionally, Gallicchio et al. (2002) found that female caregivers reported significantly higher levels of depression than their male counterparts. However, when depressive symptoms were examined, gender differences were no longer apparent. Feelings of loneliness and loss have also been cited among spousal caregivers (Beeson 2003). In another study, female caregivers were found to experience greater psychosocial distress, whereas male caregivers were shown to be at greater physiological risk (Zhang et al. 2006).

Positive Aspects of Caregiving

Despite the negative aspects of caregiving, many caregivers also reported positive effects (Andren and Elmstahl 2005), indicating the complex nature of the family caregiver role (Tarlow et al. 2004). These features included pride in fulfilling filial or spousal duties and a sense of role satisfaction and closeness with the care recipient. These positive aspects of caregiving were associated with lower levels of perceived burden and depression (Sorensen and Pinquart 2005) and with ethnic/cultural factors. For example, African American and Latino (particularly, less acculturated Latino) caregivers showed higher scores than whites on the Positive Aspects of Caregiving scale (Coon et al. 2004; Haley et al. 2004; Hilgeman et al. 2007; Mausbach et al. 2004) and on measures of subjective well-being (Pinquart and Sorensen 2005). Additionally, when daily care burden decreased over time among African American caregivers, Positive Aspects of Caregiving scores increased and depression levels decreased. Caregivers who scored higher on subjective health and higher Positive Aspects of Caregiving also reported lower levels of "bother" related to care recipient behavior, regardless of racial or ethnic identification.

Protective Factors

Several reports indicated that positive aspects of caregiving may serve a protective function (Andren and Elmstahl 2005), particularly against depression (Sorensen and Pinquart 2005). Both social support (helping with tasks) and emotional support have been cited as protective factors (Roth et al. 2005). Pinquart and Sorensen (2005) described higher levels of informal support among ethnic minority caregivers, which indicates the communal nature of some caregiving tasks, particularly among people in African American and Latino communities.

Coping effectiveness has also been shown to have a buffering effect on caregiving stress (Gottlieb and Rooney 2004). In a meta-analysis of the coping research among dementia caregivers, caregivers utilizing problem-solving and acceptance styles of coping were shown to fare better than those using other forms of coping (Kneebone and Martin 2003). In addition, caregivers who used acceptance and instrumental (problem-focused) coping strategies tended to experience fewer depressive symptoms than those using other strategies. Cultural differences also emerge in relation to caregiver coping styles. In a study by McClendon et al. (2004), African American caregivers were reported to use more "wishful thinking" strategies, such as wishing the caregiver could change the way he or she felt or wishing things were different. Use of emotional avoidance as a coping mechanism was correlated with increased depression and negative affect in white female caregivers (Spira et al. 2007). Caregivers of members of ethnic minorities were more likely to utilize cognitive coping (seeking positive aspects of caregiving) and emotion-focused coping (distractions, venting, avoidance) than white caregivers.

Assessment Tools

Assessment of caregivers is important in clinical practice. Close attention to caregiver responses can uncover caregiver stressors, whether subjective or objective; help determine resources the caregiver needs (assistance in care-

giving by visiting nurses or home health aides); and help ascertain the strengths of caregivers, including their psychological resources and coping skills. The assessment tools discussed here ascertain what emotional and physical supports caregivers need, and how caregivers view their own physical and mental health, their social supports, and their relationships. For the most part, they are adapted from extensive material on this topic developed by the Family Caregiver Alliance (2006b).

The Caregiver Health Self-Assessment Questionnaire, developed by the American Medical Association (2007a, 2007b), was created for office use to identify and provide preventive services to caregivers, monitor caregiver distress, identify the need for supportive services, and make appropriate referrals to community resources when needed. This brief assessment is a self-report scale consisting of 16 yes/no items and two global items designed to estimate emotional and physical distress (e.g., perceived stress, feelings of depression, etc.). It is available on the American Medical Association Web site in English and Spanish. Scoring instructions and suggested follow-up steps are provided. This instrument is free, easily available, quickly scored, and an excellent starting point to use in a busy office setting. However, when more time is available to assess the caregiver, the following constructs and measures are recommended.

Caregiver Stress

The Revised Memory and Behavior Problem Checklist (Teri et al. 1992) is a self-administered objective and subjective inventory to be completed by caregivers. It consists of 24 two-part questions and takes approximately 10 minutes to administer. It focuses on "observable, conceptually relevant, and potentially modifiable behaviors" (Teri et al. 1992), and yields both an overall score of the frequency of behaviors, and how "upset" or "bothered" the caregiver was as a result of a particular behavior. There are three subscale scores (memory-related, depression, and disruptive behaviors) (Teri et al. 1992), enabling clinicians to pinpoint areas in which caregivers may be challenged and areas in which intervention might be helpful for both the caregiver and the care recipient. Reliability and validity have been well established (Roth et al. 2003).

Caregiver Emotional Functioning

There are numerous screening measures for depression in caregivers and care recipients. Among these are the Beck Depression Inventory-II (Beck et al. 1996), the Geriatric Depression Scale (Yesavage 1983), and the Center for Epidemiological Study—Depression Scale (CES-D) (Radloff 1977). Due to the short, self-report nature of these depression screens, they can easily be administered to the caregiver while the care recipient is being examined.

The Geriatric Depression Scale was developed for older adults (Yesavage 1986). There are two versions, a short form (15 items, most commonly used) and long form (30 items). Both forms, in English, have been validated against other known scales for depression. The forms are also available in 28 languages at http://www.stanford.edu/~yesavage/GDS.html, but translation accuracy is not guaranteed. There is no charge for its use.

The Beck Depression Inventory-II is a screening measure for depression. It is a 21-item self-report instrument that assesses both the existence and severity of symptoms by asking the respondent to choose the response that best describes him or her over the past 2 weeks, and to rate the symptoms on a 4-point scale. (This instrument is available for purchase through The Psychological Corporation, 19500 Bulverde Road, San Antonio, TX 78259.)

The CES-D is a widely used 20-item, frequency-based, self-report measure of depressive symptoms developed by the National Institute of Mental Health. There are four separate factors: depressive affect, somatic symptoms, positive affect, and interpersonal relations (http://www.assessments.com/catalog/CES_D.htm). The CES-D can be used in a variety of settings, populations, and cultures, but consideration of ethnicity is needed, as norms may vary in different ethnic groups (http://patienteducation.stanford.edu/research/cesd10.html). The CES-D is in the public domain; the English version is available at http://patienteducation.stanford.edu/research/cesd.pdf. The instrument is available in Spanish. There is no charge for its use.

Caregiver Burden

Caregiver burden is a term used to encompass the effects of the physical, emotional, and financial tolls of providing care. The Zarit Burden Interview (Zarit et al. 1986) is a 22-question self-report on the frequency of feelings that arise from the caregiving role. It arrives at a global measure of caregiver burden. It has been translated and validated in Chinese and French (Chan et al. 2005; Hébert et al. 1993). However, some cultural groups do not endorse the concept of "burden," and so may underreport on a scale such as this, which may limit its use with ethnically and culturally diverse family caregivers (Aranda and Knight 1997).

Another measure employed to assess caregiver burden is the Screen for Caregiver Burden (Vitaliano et al. 1991). This measure was designed to assess the physical, psychological, emotional, social, and financial problems that the caregiver may experience (Rush et al. 2007). It employs questions about behaviors of the care recipient, af-

fective responses of the caregiver, financial resources, and disruption in family and social life. Scores on two aspects of caregiver burden can be derived: objective burden, which measures the level of care provided, and subjective burden, which reflects the distress that the caregiver is experiencing. There is no information about use of this measure with ethnically diverse caregivers.

Caregiver Cognitive Functioning

The Mini-Mental State Exam (Folstein et al. 1975) is a brief screening tool for cognitive function. Although it is not sensitive to minor cognitive deficits, it is useful for detecting gross cognitive impairment in caregivers. (See also Chapter 3, "Neuropsychiatric Assessment and Diagnosis," and Chapter 5, "Neuropsychological Assessment in Dementia," for screening instruments.)

Other Aspects of Caregiving

Positive Aspects of Caregiving

Positive Aspects of Caregiving is an 8-item response card assessment. Using a Likert scale, caregivers indicate their amount of agreement with positive statements about caregiving (Tarlow et al. 2004). The Yale Social Support Index (Seeman and Berkman 1988) is a 29-item self-report measure of amount and quality of social support.

Coping

We also recommend the Revised Ways of Coping Checklist (Vitaliano et al. 1985), a measure of coping strategies widely used in both research and clinical settings (Thompson et al. 2006). Coping strategies assessed include Problem-Focused Coping, Social Support Coping, Blamed Self, Avoidance, and Wishful Thinking. Each of these measures (either in total or selected components) has been used with ethnically and culturally diverse caregivers in such programs as the Resources for Enhancing Alzheimer's Caregiver Health (REACH) caregiver intervention projects (Belle et al. 2006).

Psychiatric Disorders

The Primary Care Evaluation of Mental Disorders (Spitzer et al. 1993) covers 16 diagnostic categories, of which 8 are specific to the DSM-IV-TR (American Psychiatric Association 2004) and correspond to mood, anxiety, somatoform conditions, eating disorders, and alcohol abuse in the primary care setting (van Hook et al. 1996). There are two parts: a one-page, self-administered questionnaire, followed by a structured interview that explores the positive responses to the questionnaire. Spitzer et al. (1999) developed an alternate version of this questionnaire that is entirely based on self-report. The brevity of this measure makes it practical to use with family caregivers when there is suspicion of more significant mental health problems beyond what is explainable as typical caregiver stress or distress. (Thompson et al. 2006).

Evidence-Based Interventions

Given the potentially deleterious psychological and physiological outcomes associated with dementia caregiving, there is a need for interventions that specifically target the unique problems of these caregivers. There has been tremendous growth in the past 10 years in the number of high-quality treatment outcome studies (e.g., randomized controlled trials, manualized treatments based on a coherent theory of change, increased emphasis on treatment fidelity) that have enabled identification of intervention strategies meeting criteria for evidence-based psychological treatments, as enumerated by Yon and Scogin (2007). In an earlier review by Gatz et al. (1998) of psychological treatments for older adults, only four caregiver intervention studies met evidence-based treatment criteria. In contrast, in an updated review of this literature using similar inclusion criteria, 19 studies were identified that supported the efficacy of a variety of caregiver interventions, including psychoeducational skill-building programs, psychotherapy and counseling, and multicomponent interventions (Gallagher-Thompson and Coon 2007).

Psychoeducational Programs

In general, these programs are time-limited (4–12 weekly sessions, lasting 1–2 hours), follow detailed intervention manuals, and are delivered in a group format that strives to promote new learning and/or skill acquisition. Although the emphasis is on education, these interventions have a broad impact beyond knowledge acquisition. In a quantitative review of caregiver interventions, psychoeducational treatments were shown to be one of the most efficacious forms of therapy. Caregivers showed consistent improvement on measures of burden, depression, well-being, ability/knowledge, and care recipient symptoms (Sorensen et al. 2002).

Although the specific skills taught may vary, four approaches to caregiver psychoeducation warrant evidence-based treatment status (Gallagher-Thompson and Coon 2007). They include behavioral management skills training

(e.g., Bourgeois et al. 2002), depression management (e.g., Coon et al. 2003b), anger management skills training (e.g., Steffen 2000), and the progressively lowered stress threshold model (e.g., Huang et al. 2003). Typically, behavioral management skills training teaches caregivers how to improve mood and/or manage symptoms of distress such as depression and anxiety through cognitive-behavioral strategies, which include increasing one's engagement in pleasant events, promoting relaxation through breathing exercises, or expanding participants' social support systems.

Psychoeducational interventions for depression also teach many of these same skills. Based on cognitive-behavioral treatment methods for depression (Beck et al. 1979; Lewinsohn 1974), these interventions usually also include skill-building components that help caregivers identify and challenge cognitive distortions and automatic thoughts that may maintain or give rise to depression. In a similar way, anger management skill training uses many of these same cognitive-behavioral techniques, with the addition of skills designed to teach caregivers to identify antecedents or triggers of anger and develop greater awareness of their own level of frustration (Ecton and Feindler 1990; Novaco 1985). Rather than focusing directly on caregiver symptoms, psychoeducational programs based on the progressively lowered stress threshold model concentrate on teaching skills to manage stressors, such as changes in routine or multiple and competing stimuli, that might interact with the care recipient's physical condition to exacerbate problem behaviors (Hall and Buckwalter 1987).

Formal Psychotherapy

Psychotherapy is effective for more severely distressed caregivers (Brodaty et al. 2003; Sorensen et al. 2002). Psychotherapy improves symptoms across a variety of domains, including depression, caregiver burden, and choice of coping skills (Sorensen et al. 2002). Although treatment studies have examined interventions for caregivers based on several different theoretical orientations, the majority have involved cognitive-behavioral therapy (CBT). Of the three studies that met evidence-based treatment criteria, all used CBT or were strongly CBT-based (Gallagher-Thompson and Coon 2007). This approach conceptualizes distressing emotional reactions, such as depression and anxiety, as arising from problematic patterns of thinking that may be rather automatic. Treatment involves targeting thoughts that give rise to these feelings and working with the caregiver to develop alternate, more adaptive, less stress-inducing ways of thinking. Treatment may also include managing symptoms through relaxation, working on problem solving, and encouraging more frequent engagement in pleasant events (Beck et al. 1979).

Multicomponent Interventions

Given the multitude of challenges facing family caregivers, multicomponent interventions that include combinations of various treatments such as psychoeducation, respite care, and support groups, have been developed and tested with success (Gallagher-Thompson and Coon 2007; Sorensen et al. 2002). Though one recent meta-analytic study suggested that multicomponent interventions might be less effective than psychoeducation or psychotherapy alone (Sorensen et al. 2002), a different conclusion was reached in subsequent reviews, which judged these combined treatments to be some of the most effective (Shulz et al. 2005).

Since the publication of these reviews, the REACH projects have been completed and major results published. The REACH program is one of the largest multicomponent intervention studies conducted in the United States. The first phase included 1,222 caregivers across seven different sites (Schulz et al. 2003). Although the type of treatment differed at each location, most included psychoeducation/skill-building interventions, often accompanied by efforts designed to strengthen caregiver social support systems. Despite the variability across sites, overall results showed that active interventions were superior to control conditions in reducing caregiver burden. These effects were most pronounced for women and persons with lower educational levels. With regard to depression, Hispanic caregivers, nonspouses, and those with lower educational levels showed the greatest treatment-induced gains. Finally, interventions that promoted active engagement of caregivers were found to be most effective (Belle et al. 2003; Schulz et al. 2003). The diverse effects among subgroups of participants highlight the varying needs of different caregivers, and underscore the potential advantage of an intervention strategy that could flexibly address the unique combinations of issues they face.

In an effort to address these varying needs, a second phase (REACH II) delivered a structured, yet individually tailored, multicomponent intervention to 642 Hispanic/Latino, white, and African American caregivers across five sites (Belle et al. 2006). Depending on one's level of risk as assessed by baseline measures, the actual program that each caregiver received could be tailored to address five possible target areas: depression, burden, self-care, social support, and problem behaviors. Consistent with a CBT framework, these targeted problems were addressed using a variety of strategies such as information giving, didactic instruction, role playing, problem solving, skill training, stress management techniques, and telephone support groups. For the majority of caregivers, these interventions improved quality of life (as operationalized by measures that corresponded to each of the five target areas) com-

pared with those in the control condition, particularly among white and Hispanic/Latino caregivers and African American spousal caregivers. In both REACH projects, all interventions and assessment materials were available in Spanish, bilingual/bicultural staff was employed, and considerable individualization of the interventions was employed to make them responsive to diverse cultural views of dementia and caregiving (Gallagher-Thompson et al. 2003a, 2003b).

In addition to these findings, other multicomponent interventions have also demonstrated positive results. Mittelman et al. (1995) examined the efficacy of a three-component treatment with 406 caregivers that involved individual and family counseling sessions focused on improving communication and reducing problem behaviors, and providing psychoeducation, participation in support groups, and ad hoc counseling. This program had a positive impact across a variety of domains including depressive symptoms, appraisals of care recipients' behavioral problems (Mittelman et al. 2004), and rate of nursing home placement (Mittelman et al. 1996).

Both the REACH program and the Mittelman approach will be disseminated by the U.S. Administration on Aging and by such advocacy groups as the Rosalynn Carter Institute for Family Caregiving. It is anticipated that based on these efforts, more training opportunities, materials, and technical support will become available.

Other Interventions With Less Empirical Basis

Although psychoeducation, psychotherapy, and multicomponent interventions have the strongest empirical support, these three modalities do not represent all of the treatment options available to caregivers. Numerous other interventions seem promising but remain relatively untested. In some cases, the treatments have been shown to be less effective overall, but are still routinely used because they contain other important features, such as their accessibility or cost effectiveness. A complete description of all these interventions is not possible, but several novel interventions are worth noting, along with a brief discussion of some of the more widely used treatments.

The Savvy Caregiver Program

Because little effort has been made to package and disseminate psychosocial interventions in a way that can be easily digested and used in everyday practice settings, Hepburn et al. (2003) developed the Savvy Caregiver Program—a package of intervention training tools, which includes a trainer's manual, caregiver manual, and CD-ROM. These materials were designed to facilitate psychoeducational interventions that have been efficacious across several outcome measures (Hepburn et al. 2001; Ostwald et al. 1999). Initial findings from a pretest-posttest field trial suggest that this training protocol could be effectively used by a variety of practitioners (Hepburn et al. 2003).

Powerful Tools for Caregivers

Important barriers to caregiver education are lack of transportation, health problems, and overwhelming schedules. The Powerful Tools for Caregivers program merges familiar psychoeducational interventions for caregiving with new technology. Available on the Internet, this program is a Web-based, 6-week educational program that provides tools for managing self-care, coping with common stressors, and improving communication. Pretest-posttest data suggest that this program improves caregivers' level of confidence, and reduces depressive symptoms and reactions to care recipients' memory and behavior problems (visit www.matherlifeways.com/re_ptcbenefits.asp, for a complete description).

Support Groups

Free support groups are offered throughout the world by such community agencies as the Alzheimer's Association (Thompson et al. 2006). There is a great deal of variability in these groups in terms of the level of training given to group facilitators and the frequency and duration of meetings. Therefore, the groups may be variable in effectiveness and educational value. The typical goal of support groups is to expand one's social support system, foster emotional expression, and exchange information. Although a recent review suggests that participation in support groups may help caregivers in reducing feelings of isolation and increasing knowledge, these groups may be less effective for difficulties such as depression, overall sense of well-being, or management of behavioral problems of the care recipient (Sorensen et al. 2002). Despite mixed empirical support, support groups remain popular because of their low cost, widespread availability, ease of application, and minimal burden to caregivers. In addition, the Alzheimer's Association provides a great deal of free information at www.alz.org, including a large amount of material in languages other than English. Appendix J contains information concerning other organizations that offer education and support for caregivers.

Care/Case Management

Care or case management is an approach that identifies caregivers' needs and links them to relevant community re-

sources while providing ongoing emotional support and monitoring. This form of intervention is widely available and is often supported by state, county, or federal funding. As a result, case management services are a resource available to underserved populations. There are limited empirical studies of this type of intervention. A care consultation intervention that included information about available community resources and psychoeducation was compared to treatment as usual offered by a large managed care system. Overall, those who received care consultation tended to be less depressed, experienced less strain, and were less likely to rely on some managed care services (Bass et al. 2003).

Day Care/Respite Care

Adult day care centers for persons with dementia can give caregivers respite. Patients attend these programs from 1–5 days a week. Respite care has generally had only modest positive impact on caregivers' feelings of depression and burden (Sorensen et al. 2002), but a 4-year study suggests that participation in day care might delay nursing home placement of Alzheimer patients (Wilson et al. 2007). The same study found that use of day care was greater among ethnic minority groups and those with lower levels of education, whereas white care recipients were more likely to be placed in a nursing home over the 4-year period of the study. In addition to these empirical findings, day care might provide a transitional experience that enables care recipients and family caregivers to better adjust to a nursing home placement when it becomes necessary. Notwithstanding these positive effects, day care is an added financial burden to families.

Psychopharmacological Treatment for Caregiver Distress

Medication management of psychiatric problems in caregivers of dementia patients is important for maintaining a stable environment for the dementia patient. After due consideration for the boundaries among the clinician, patients, and caregivers, management of caregiver problems should be addressed as carefully and completely as possible.

Many practitioners are able to provide support within the context of their treatment of patients, but others find it desirable to refer to other professionals. Referral to a psychiatrist may be justified and, in the case of an elderly caregiver, a psychiatrist trained in the care of the elderly may be especially useful. The most common problems of caregivers are depression and sleep disturbance.

Depression

Major depression occurs in approximately 20% of caregivers (Cuijpers 2005); symptoms of depression are even more widely reported, as assessed by self-report scales (Mittelman et al. 2007). Detection is important because depression reduces the quality of life of caregivers and increases the likelihood of potentially harmful behavior by caregivers (Beach et al. 2005). The Geriatric Depression Scale (Yesavage et al. 1983) is a useful self-report screening instrument. Treatment of depression is guided by the principles of geriatric psychopharmacology: start with low doses, increase dosage slowly, and persist in using the drug over time. The use of antidepressant drugs for symptoms of depression is similar in both caregivers and persons with dementia, and the psychopharmacological treatment of depression is addressed in Chapter 16 of this volume, "Pharmacological Treatment of Neuropsychiatric Symptoms."

Sleep

Sleep difficulties are a general problem among the elderly, and are particularly problematic for caregivers when the cared-for patient is not sleeping. Thus, the first priority is helping the patient with dementia to rest at night. For the caregiver, the first recommendation for sleep problems should be a full review of sleep-hygiene principles. It is risky to give caregivers medication that will leave them unresponsive to patients' needs and safety during the night, so maximum efforts should be made to avoid caregiver use of hypnotics.

When recommending a sleep aid, the first consideration should be the use of melatonin. Melatonin is a very safe substance, but its half-life may be only 90 minutes, so that if 3 mg or 6 mg helps initiate but not sustain sleep, an extended-release preparation is available that might work more effectively.

Trazodone is often helpful for sleep, starting at 25 mg before bedtime, increasing by 25 mg every other night until adequate sleep occurs or morning drowsiness becomes a problem. The possibility of priapism should be explained to men, but it is rare in the elderly.

Anxiety and Related Problems

In general, behavioral approaches to the management of anxiety are more effective than medications. For caregivers experiencing anxiety, the best first approach is to try to improve their support system. Attention to a possible depressive component is a primary issue to be addressed before considering antianxiety medications, and the same is true for use of hypnotics.

When prescribing antianxiety medications, there is a great concern that the medications not impair caregivers' capability of managing their patients. In this regard, trazodone is also of use in doses of 25–50 mg. The 3–5 hour half-life of trazodone may require its use every 3–6 hours during the day, with a maximum dose of 300 mg/day. Buspirone is generally ineffective. Benzodiazepines, which are relatively contraindicated for persons with dementia, may also be considered. They should be used as a last resort because they could impair cognitive function and cause ataxia and falls in older adult caregivers. These medications also tend to cause more anxiety during rebound and can be associated with dependence.

Another issue in treating anxiety is the presence of posttraumatic stress disorder (PTSD). PTSD should be suspected after discovery of a history of a stressful event or the presence of recurring nightmares. Trazodone and prazosin have both been useful in the suppression of PTSD nightmares, and can be used during the daytime to diminish anxiety and hyperactive startle reflexes. SSRIs are also useful in PTSD, and propranolol can also be useful to decrease PTSD-related daytime anxiety.

Caregiver Cognitive Impairment

A substantial concern in the management of dementia patients is that the caregivers, especially when they are spousal caregivers, may be cognitively impaired as well. In addition to the obvious concerns about caregivers being able to follow instructions and manage issues such as patient medications and finances, there is also concern about potentially harmful behaviors of cognitively impaired caregivers toward their patients (Miller et al. 2006). Clinicians should maintain concern regarding signs of significant caregiver cognitive impairment (Ashford et al. 2007) and refer for full evaluation if suspected.

Long-Term-Care Placement

Although maintaining dementia patients in their homes may be best for the patients' functioning, there may come a time when the duties and stressors of caregiving fall beyond the caregiver's abilities. The later stages of dementia can be physically and emotionally challenging, even for the best of caregivers, and long-term-care placement may in many instances be the best option for caregiver and care recipient alike.

In the United States, the cost of assisted living for dementia patients is, on average, $51,204 per year, while individual nursing home placement for dementia patients costs, on average, $79,935 per year (MetLife Mature Market Institute and Life Plans Inc. 2008). In 2005, $90 billion was spent on nursing home care in the United States. At that time, spending was projected to increase to $160 billion by 2010 and $189 billion by 2015 (Alzheimer's Association 2008).

Mittelman et al. (2006) found that tailored individual and family counseling helped to delay nursing home placement. Included in the counseling were resources referrals and encouragement of caregivers to attend local support groups. Additionally, the REACH investigators (Belle et al. 2006) reported that caregivers who were confident in their abilities to care for their care recipients and mentioned greater positive aspects of caregiving were more likely to delay nursing home placement.

Knopman et al. (1999) found that functional impairment of the dementia patient was the strongest predictor of nursing home placement, but a number of other factors were also relevant, including increased need for skilled care, declining caregiver health, and increased care recipient problem behaviors (Burh et al. 2006). In addition, cultural values play a role in determining nursing home placement. For example, white caregivers were found to place their family members in nursing homes sooner than their Latino (Mausbach et al. 2004) and African American (Yaffe et al. 2002) counterparts, regardless of the socioeconomic status, behavior, and functional impairment of the care recipients and the caregivers' subjective experiences of caregiving (Stevens et al. 2004). However, low levels of acculturation, increased depression, and positive aspects of caregiving in spousal Latino caregivers have been shown to decrease time-to-placement of a dementia care recipient (Stevens et al. 2004). However, Latino caregivers with less positive views of caregiving and higher levels of depression were more likely to institutionalize than both white and Latino caregivers who reported greater positive aspects of caregiving (Gaugler et al. 2006; Mausbach et al. 2004). Within the African American community, however, heavily burdened caregivers of older, male care recipients were more likely to place their loved one sooner (Gaugler et al. 2004; Yaffe 2002).

KEY POINTS

- Family caregivers of dementia patients vary in many dimensions, such as gender, ethnicity, cultural background, and relationship to care recipients.
- Caregiver management of dementia patients is influenced by cultural and economic factors, in addition to specific issues related to care recipients.
- Dementia caregiving is the most stressful kind of informal caregiving and increases vulnerability to physical and psychological ill health.
- There are many opportunities to support caregivers through psychological and psychosocial interventions that will help them maintain adaptive functioning as caregivers for a longer period of time.
- Adequate caregiver support may help delay or prevent long-term-care placement.

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CHAPTER 21

Legal Issues

Lawrence A. Frolik, J.D., L.L.M.

Our legal system operates on the assumption that adult individuals are capable of making decisions on their own behalf. The law permits and supports the rights of individuals to make the decisions that control their person and property. If, however, because of Alzheimer disease or other mental impairments, an individual has lost the mental capacity to make decisions, that individual cannot participate in much of life. Mentally incapacitated individuals cannot make a legally binding contract, such as an admission agreement to an assisted living facility; cannot control their finances, such as selling stocks or buying real estate; and cannot give informed consent to medical decisions, such as agreeing to surgery (Frolik and Radford 2006; Meisel and Ceminara 2004). Although mentally impaired individuals cannot make such decisions, the law has devised ways to create surrogate or proxy decision makers who can make decisions on their behalf.

Individuals can appoint such surrogate decision makers by making use of a *durable power of attorney,* and can create trusts and joint property arrangements that permit others to handle their financial affairs. Absent the individual creating a surrogate decision maker, the law can provide one by the use of guardianship or conservatorship. Health care decisions can be made by guardians or by statutorily created proxy decision makers. And, of course, in many instances the formal legal requirements are ignored, as the spouse or family of the mentally incapacitated person simply makes decisions for him or her with little or no legal basis for doing so.

Guardianship and Conservatorship

For hundreds of years, the law has responded to the need for surrogate decision makers for mentally incapacitated persons by appointing guardians and conservators (Frolik 1981). The process is referred to as *guardianship* or *conservatorship*. In some states, guardianship refers to decisions made about the health care and residence of the mentally incapacitated person, whereas conservatorship refers to decisions made about that person's property. In other states, the term "guardianship" is used to describe a substitute decision maker for both health and property. (In Louisiana, guardianship is referred to as "interdiction.") The substitute decision maker is appointed by a court and is usually referred to as a guardian or conservator, whereas the mentally incapacitated person is referred to as a *ward*, or an *incapacitated* or *incompetent* person (York 2006).

A state judicial proceeding is required for the appointment of a guardian, and the laws governing guardianship vary from state to state. There is no federal law of guardianship. Even though state laws differ, however, in general they address similar issues. In almost all cases, guardianship is an involuntary procedure imposed by the state on incapacitated persons for the protection of their person and property (Fell 1994). Although individuals can ap-

point agents under a *power of attorney* to handle their affairs, most have not done so prior to the onset of the incapacity, when it is legally too late to do so. Consequently, guardianship is then the only solution.

What Level of Incapacity Justifies a Guardian?

State law determines who needs a guardian. Even if family and friends believe that an older, cognitively impaired person needs a guardian, they must file a petition with the appropriate court asking that it declare the person in need of a guardian. When making that determination, the court will examine the evidence presented to see if the individual meets the state definition of being incapacitated. Although the laws of the various states differ, a common formulation is that a person who needs a guardian is someone who lacks the capacity to make rational decisions. The test is whether the person has the *capacity* to make *rational* decisions, not whether the person makes *responsible* decisions. Because a person makes foolish or irrational decisions does not mean he or she is legally in need of a guardian. But individuals who are incapable of making rational decisions should not be making critical decisions about their person or property, and legally they cannot do so. They need the protection of a guardian who will make decisions for them.

The law has varying requirements of capacity for different acts (Frolik and Radford 2006). Many older persons with diminished capacity due to Alzheimer disease may still have sufficient legal capacity to make all the decisions about their lives; or they may have the capacity to make some choices but not others. The determination of whether an individual has enough capacity to make a particular decision is a legal, not a medical determination (Johns 2004). Although evidence of an individual's medical condition is relevant to the legal determination, in the end, the standard of capacity is a legal one. Mental capacity, for legal purposes, is a continuum. As their incapacity deepens, individuals lose the right to make decisions that require a greater degree of insight and rationality. The legal question is whether a person has the capacity to make a determination about the particular act in question. For example, the state of Pennsylvania defines an incapacitated person as follows:

> An adult whose ability to receive and evaluate information effectively and communicate decisions in any way is impaired to such a significant extent that he is partially or totally unable to manage his financial resources or to meet essential requirements for his physical health or safety. (20 Pa. C. S. § 5501 [2008])

Different states use their own language to define mental incapacity, but the intent is the same: to define the level of incapacity that so interferes with the ability of persons to care for their persons or property that they need a guardian. To care for property, individuals must have enough capacity to be able to make a valid contract, which includes activity such as making or signing an agreement, making purchases, paying bills, and directing and managing investments. The test of contractual capacity, the ability to manage financial resources, is whether a person has sufficient capacity to reasonably understand the nature and effect of the action he or she undertakes (Frolik and Radford 2006). This is considered one of the highest, if not the highest, level of capacity characterized by the law. Many cognitively impaired persons lack that level of capacity and are unable to manage their financial affairs, and so may be in need of a guardian. For example, Adam, who suffers from Alzheimer disease, can no longer understand how to manage his rental properties. He forgets to collect the rent and cannot remember what maintenance is needed. He is someone who could potentially be considered to need a guardian.

Interestingly, the level of capacity needed to write a valid will is lower than that required to manage one's property (Leslie 1994). The burden of showing a lack of mental capacity requires clear and convincing evidence (Succession of Polk 2006). Courts have repeatedly found that an individual under a guardianship may still be capable of making a valid will. Although guidelines vary from state to state, *testamentary capacity*, or, a person's ability to understand he or she is making a will, can be proven by meeting the following four requirements:

- The person must understand the nature of the act; that is, that he or she is signing a will.
- The person must have knowledge of the extent and nature of his or her property.
- The person must know the identity of his or her potential heirs; that is, spouse, children, and other close relatives.
- The person must understand how the will distributes his or her property.

The rule, regarding the "extent and nature" of his or her property, is satisfied if the individual has a general understanding of what he or she owns. This is a much less stringent standard than the capacity required to manage one's financial resources. For example, Ben, age 88 years, with early dementia, can write a will, so long as he is aware that he has substantial assets, even though he is not sure as to their exact value. But he will need a guardian if he has forgotten that he has a brokerage account with Acme Inc., a checking account with Beta Bank, and a safe deposit box

filled with gold coins in the Tau Trust Co. Moreover, making a will only requires that the individual have capacity for the short period during which he or she signs the will. For example, Betty, whose cognition waxes and wanes, may sign a valid will during a moment of clarity, even if she soon declines into a confused, incapacitated state of mind.

The degree of capacity required to make decisions about an individual's person requires that the individual have enough capacity to make the decisions necessary to meet essential requirements for health or safety (Willis 1996). If Carol, for example, is living alone in squalor, it may evidence that she lacks the mental ability to care for herself and her surroundings. Or, if Cathy, age 90 years and suffering from dementia, is no longer able to understand what her doctor tells her about treatment options for her cancer, she needs a guardian who can work out a treatment plan for her with the physician.

Making health care decisions requires a high degree of capacity, because the patient must be able to give informed consent to proposed medical treatment. That requires that the individual understand his or her medical condition, the proposed treatment, the benefits and dangers of that treatment, and possible alternate treatment scenarios (Meisel and Ceminara 2004). Cognitively impaired persons often lack the ability to comprehend their condition or remember what they are told; they are even less likely to be able to reasonably weigh the pros and cons of the proposed treatment.

Many state statutes define *mental incapacity* in terms of individuals' behavior rather than their medical diagnosis (Johns 1999). Having a diagnosis of Alzheimer disease does not mean that the individual lacks mental capacity and is in need of a guardian. Rather, it is *how* the individual acts that is determinative.

Who Determines Whether an Individual Is Incapacitated?

All persons are presumed to be legally competent; the burden of proof is on those who claim that an individual is incapacitated. Only a court (usually a judge, but sometimes a jury) can make a determination of legal incapacity, and the court relies heavily on the behavior of individuals in determining whether they are mentally incapacitated. Testimony of lay witnesses and nonexperts, such as family and friends, is usually introduced to prove that an individual's behavior demonstrates mental incapacity and an inability to care for him- or herself. Although in theory, lay testimony such as that given by family and friends might be enough to establish proof of incapacity, in practice, expert testimony is almost always required. Testimony by a geriatric psychiatrist would certainly be the best evidence, but courts will accept the testimony of almost any medically trained individual. Family or personal physicians often testify as to the mental capacity of their patients despite their lack of expertise in disorders of cognition (Frolik 1999).

Many state laws specifically require medical support for a finding of incapacity, and, in practice, courts almost always require it. Medical testimony, which can be given by a physician, psychiatrist, psychologist, or nurse, is used to prove that the individual is in fact incapacitated, and not just acting in an eccentric or idiosyncratic manner (Gardner 2006).

The question of incapacity is determined as of the date of the hearing. An individual might have had mental capacity the previous week, but that is irrelevant to whether the person has capacity on the date of the hearing. Usually, no petition requesting a determination of incapacity and the appointment of a guardian will be filed until the petitioner believes that the individual is incapacitated. Still, the evidence of the incapacity should be as recent as possible, and the petitioner should offer proof that the individual has not improved since the date of the medical examination that forms the basis for the allegation of incapacity. The examining physician, for example, could testify that she observed evidence of an irreversible impairment.

Types of Guardianships

Guardianships can generally be sorted into one of three categories. *Guardianship of the estate,* or, as it is also known, conservatorship, is limited to substitute decision making for matters concerning the incapacitated person's property, including assets such as a bank account (known in law as an estate.). *Guardianship of the person* gives the guardian control over decisions affecting the personal well-being and care of the incapacitated person, such as where to live or whether to consent to medical treatment. *Plenary guardianship* grants the guardian the power to make decisions over both the incapacitated person's property and person (Frolik 1981). The existence of different kinds of guardianship reflects the understanding that a person may be competent in one area and incompetent in another. Courts are often more willing to appoint a guardian for the person's property because of the need to protect the property from waste or fraud. Conversely, the court may be very sympathetic to cognitively impaired individuals who want to continue deciding where they live, because this decision is essential to a sense of personal autonomy.

In the past, guardianship was thought of as an either/or proposition: the individual either did or did not have the required competency. Today, individuals are thought of as having varying degrees or types of capacity, which can create a need for substitute decision making for some, but not

necessarily all, aspects of their lives. For example, an individual may be able to handle smaller amounts of money, but may have lost the capacity to handle investments. In the past, the only option would have been to appoint a guardian of the estate, even though it would have been overly restrictive of the individual's autonomy. Today, in almost every state, the court has the option of appointing a *limited guardian* with powers tailored to meet the needs of the ward (Frolik 1998). Limited guardianship aims to not intrude on the individual's life more than is necessary. Because losing the right to make decisions for oneself results in a serious diminution of independence, a limited guardianship attempts to minimize that loss while still providing the protection of a substitute decision maker.

Procedural Issues

Filing a guardianship petition with the appropriate court is the first step in asking for a guardianship. Courts have no power to initiate guardianship proceedings or to appoint a guardian unless a proper petition has been filed. In almost all states, any interested person may file a petition requesting that the court find that someone is legally incapacitated and ask the court to appoint a guardian. Most petitions are filed by spouses, adult children, relatives, friends, or concerned neighbors. Institutions such as social service agencies and hospitals also frequently file petitions, if no family member is available or willing to do so.

State law and local court rules determine the contents of a guardianship petition. In general, the petition must name the alleged incapacitated person; the cause, nature, and extent of the incapacity; the type of guardianship sought (person or property, limited or plenary); and the name of the proposed guardian. Most courts will not accept a petition unless it identifies a proposed guardian or guardians. Included in the petition will be a list of the nature and value of the alleged incapacitated person's property, the source of his or her income, and the person's address and living arrangements. Some states require the petition to explain why no less restrictive arrangement is appropriate. Some also require the petition to explain how guardianship will meet the needs or solve the problems of the alleged incapacitated person. If a guardian of the person or a plenary guardian is sought, the petition may have to describe what actions the guardian expects to take. If a limited guardianship is sought, the petition must state what particular powers should be granted to the guardian. State law usually provides that guardianship petitions be filed in the court with jurisdiction over probate matters in the county in which the alleged incapacitated person lives or in which he or she is "present." For example, Darleen lives in Alpha County, but after a recent stroke has been living with her daughter in Beta County. Most states would permit a guardianship petition to be filed in either county.

Interestingly, the alleged incapacitated person is not always present at the guardianship hearing. If the individual is absent, it is usually because of concerns for his or her health or because the person's presence would serve no purpose, such as in the case of a comatose individual. Still, most courts feel more comfortable seeing the alleged incapacitated person, and the judge may even hold the hearing in a nursing home if that is where the alleged incapacitated person resides.

To assist the courts in understanding the circumstances that gave rise to the filing of the petition, several states require or permit the use of a court visitor. Even if not required, many courts routinely send a representative to visit alleged incapacitated persons in their place of residence. The court visitor reports to the court regarding the alleged incapacitated person's physical and mental condition, his or her reaction to the possibility of having a guardian, and whether his or her physical or mental condition permits a personal appearance at the hearing. The visitor also often interviews the petitioner and the individual nominated to act as guardian in order to understand why the petition was filed, and whether the proposed guardian is capable of carrying out the responsibilities of the position. The visitor's report can play a significant role in determining whether the court will grant a guardianship.

Before family members file a guardianship petition, they should realize that the hearing is open to the public and that the alleged incapacitated person will most likely be represented by an attorney. Such a situation may mean that the hearing will be contentious. At a minimum, the court will insist on a full airing of the mental problems of the person. As a result, a guardianship hearing can be a painful or upsetting experience for many family members.

When appropriate, courts can appoint *temporary* or, as they are also known, *emergency guardians*. Almost every state guardianship statute permits the rapid appointment of a guardian, if circumstances dictate. For example, if an individual's property is at risk because the person with dementia is easily persuaded to part with it, the court can quickly appoint a guardian of the property to take control to protect it from harm or loss. To expedite the appointment of a temporary guardian, many state statutes streamline procedural requirements. For example, formalities of notice may be relaxed and time limits compressed.

Selection of the Guardian

If the petition is granted and the individual is found to be incapacitated, the court will almost always appoint as guardian the person nominated in the guardianship peti-

tion, unless there is some good reason not to do so (Jorgensen 2007). For example, if the proposed guardian lacks the ability to assume the responsibilities of a guardian or if, in the past, he or she behaved badly toward the incapacitated person, the court will appoint someone else to act as guardian. Sometimes, courts appoint a guardian of the property, such as a bank, and, also, a family member as guardian of the person, in recognition of the different abilities of those selected as guardians.

If the proposed ward has at least some capacity, the court may inquire whom the proposed ward would want named as guardian. Courts do not want to appoint as guardian an individual that the ward dislikes or distrusts, if that can be avoided. Hostility between a guardian and the ward does not portend well for a successful guardianship.

Occasionally, the need for a guardian is clear, but it is less clear whom the court should appoint. Adult children can sometimes be very competitive about who should be appointed guardian. Sometimes, the children do not trust each other with the parent's property, fearing that the sibling will steal or misuse it. At other times, the children disagree about what is the best course of medical treatment, each accusing the other of not acting in the best interests of the impaired parent. The children may also disagree about where the parent should be housed. One child may think that a nursing home is the best residence, whereas the other child may believe that care should be provided in the parent's home. Both want to be named guardian so that they can do what they believe is best for their parent. When faced with family conflict, the judicial reaction may be to name a nonfamily member as guardian. In some cases, the court names the children as joint guardians so that they must agree on any course of action. A third solution is to name one child as guardian, but require that child to obtain judicial approval of controversial acts such as selling the parent's house and placing him or her in a nursing home.

Realistically, the court's choice of whom to appoint as guardian is limited to those persons or entities that are willing to act in that capacity, because the court has no power to compel anyone to accept appointment as guardian. An adult child, for example, cannot be forced to act as guardian for an incapacitated parent. If no one else is available, the court may have the power to appoint a guardian who will be paid by the state. Often, such guardians are lawyers whom the court knows and respects. In recent years, state laws have been liberalized to permit nonprofit entities to be appointed as guardians. Consequently, some social service entities now provide guardianship services for which they are paid, either from the estate of the incapacitated person, or by the county or state. Several states have created *public guardians* to act as the guardian of last resort when no private individual or entity is available. Public guardians are agencies, offices, or public officials whose job is to act as guardian of the estate or person. Some are employed by the state or the county; others are hired on an as-needed basis (Barnes 2002).

Paying for the Guardianship

Guardianship is expensive. Almost all guardianship petitions are filed by a lawyer, who is usually hired by the person seeking to be named the guardian, or by some other interested person. In addition to court fees (usually fairly modest), a physician or other qualified professional will have to be paid for preparing an affidavit that affirms the potential ward's incapacity. Other possible costs include hiring a social worker to prepare a plan for how to care for the alleged incapacitated person and the fees of other possible witnesses. If the court uses a visitor or guardian *ad litem*, he or she will also be paid a fee. If the case is appealed, additional legal costs will be incurred. If the guardianship petition is successful, most courts will order that all costs be paid by the ward. The guardian may also charge a fee for his or her services, subject to court approval. Banks that act as guardian expect to be paid for their efforts, but family members or friends who serve as guardians are not normally paid for their time. As with all guardians, however, any out-of-pocket expenses that they incur will be reimbursed from the assets of the ward (Frolik and Radford 2006).

Duties and Powers of a Guardian

Once appointed, a guardian is accountable to the court and is required to inventory the assets of the ward and keep a record of all income and expenses. The guardian of the person must be prepared to explain how he or she cared for the ward and whether the guardianship should be continued. Many states require annual or periodic accounting by the guardian of the estate about the income received by the ward and a detailed description of how expenditures of the ward's assets were spent. All states require a final financial accounting at the end of the guardianship, whether because of the termination of the guardianship, resignation of the guardian, or death of the ward (Hurme 2002).

In carrying out their responsibilities, guardians are expected to act in the best interests of the ward: that is, to make decisions in a manner consistent with the ward's desires, values, aspirations, and lifestyle (Frolik 1981). Many state laws require the guardian to consult with the ward before making significant decisions. If the ward is too affected by dementia to indicate a preference or never expressed one, the guardian should act as a person without

dementia would act under the circumstances. Guardians who fail to carry out their obligations may be removed by the supervising court or ordered to act in a more appropriate manner. Generally, state law permits any interested person, including the ward, to petition the court and ask for removal of guardian.

Guardians of the person or plenary guardians typically have the power to decide where the incapacitated person will live. For example, the guardian may conclude that the incapacitated person can no longer live alone and may help the individual to move into some type of assisted living arrangement. In many cases, the incapacitated person needs to move into a nursing home, but lacks the capacity to sign the admission agreement with the facility. Whether a guardian may move the incapacitated person into a nursing home without prior court approval depends on state law.

A guardian of the property of the incapacitated person has extensive powers over the person's assets. The guardian must take charge of the assets of the incapacitated person, collect the income, and pay for his or her support and maintenance. The guardian may have the right to engage in giving away assets as an aspect of estate planning or even planning to create eligibility for Medicaid payment for long-term care (Fliegelman and Fliegelman 1997). Unless specifically ordered by the court, the guardian of the property is governed by the state statute, which is often fairly specific as to how the guardian can invest the assets of the incapacitated person (Frolik 2002).

Although guardians of the person and plenary guardians have wide latitude to act, there are limits. Normally, a guardian cannot vote for the incapacitated person, cannot consent to his or her marriage, in most states cannot consent to a divorce on behalf of the incapacitated person, and, in some states, may not consent to termination of life-sustaining medical treatment without prior court approval.

Guardianships automatically terminate upon the death of the incapacitated person. The death, incapacity, or resignation of the guardian, however, does not terminate the guardianship, because the supervising court will merely appoint a successor guardian. Normally, no guardian will be permitted to resign unless there is an available successor guardian, since the incapacitated person cannot be left in the legal limbo of lacking legal capacity to make decisions, and also lack a substitute decision maker.

Durable Power of Attorney

Cognitively incapacitated persons do not require a guardian if they have planned for the possibility of incapacity or if, upon first showing signs of cognitive impairment, they are encouraged to plan for more serious incapacity. The solution is to sign a *durable power of attorney,* a document by which an individual, the principal, appoints another person to be his or her agent (also known as an *attorney-in-fact*) to act on behalf of the principal in the event that the principal becomes mentally incapacitated. Every state has a statute that permits an individual to create a durable power of attorney, which is called "durable" because the power is not affected by the mental disability of the principal, unlike the traditional power of attorney that is terminated if the principal becomes incapacitated (Frolik and Radford 2006). Not only does a durable power of attorney greatly lessen the need for a guardianship, it also preserves the privacy of the principal because the document is not a public record (Whitton 2007).

State laws vary somewhat as to what is required to create a valid durable power of attorney, but all states require the power to be documented in writing and signed by the principal. Most states require the document to be witnessed, and some require the signatures to be notarized. The extent and duration of the power of the agent is dependent on the authority granted in the power of attorney. In some states, the agent's authority is not terminated until he or she has received notice of the revocation or termination of the power of attorney. The power is also terminated upon the resignation, death, or mental incapacity of the agent, although the power will usually name an alternative agent, should any of those events occur.

State law determines who can execute a durable power of attorney. Typically, the individual must be an adult and have the requisite level of mental capacity, which is the same as that required to enter into a contract: that is, having sufficient mental capacity to reasonably understand the nature and effect of the act. This standard is consistent with the agent being able to sign contracts on behalf of the principal. Consequently, it is not surprising that the law requires the principal to have the mental capacity necessary to enter into a contract. Mere physical frailness or disability, however, does not mean that the principal lacks the capacity to sign a valid power of attorney, as long as the person's mind is clear. State law usually permits a signature by a mark, and may even permit another to sign for the principal if the act is duly acknowledged and witnessed.

State Statutory Requirements and Recommended Contents

When drafting a durable power of attorney, the applicable state law must be examined and followed; if the requirements of the state in which the document is executed are not met, the power may not be valid. Many states have

model durable powers of attorney forms which, though usually not mandatory, are commonly used.

Regardless of the state requirements for a valid durable power of attorney, it is advisable to have the document signed by two witnesses, notarized, and dated. Multiple copies should be signed that can be provided to third parties, such as banks and stock brokers. In many jurisdictions, it is common to record the power with the county register of wills or property (if the power grants the agent the right to sell real property). Generally, the power names an agent and a backup agent in the event that the primary agent dies, becomes incapacitated, or cannot act as agent for some reason.

It is also advisable to have the agent sign the document and accept the appointment as an agent, acknowledging that he or she understands the obligations and responsibilities of an agent. By statute, for example, Pennsylvania requires agents to sign an acknowledgment that they understand that they must

- Act for the benefit of the principal;
- Maintain the assets of the principal, separate from theirs;
- Exercise reasonable caution and prudence; and
- Keep full and accurate records of all actions, receipts, and disbursements (20 Pa. C.S. § 5601[d] [2008]).

Having the agent sign such an acknowledgment makes sense, because it alerts the agent to the gravity of the responsibility and the burdens of the obligations being assumed. Although some states now make all powers of attorney durable unless otherwise stated, the practice is to include at the beginning of the document that the power is durable and not affected by the mental incapacity of the principal.

State law defines what powers can be granted to an agent, but the principal can tailor the document to the particular powers that should be granted with the goal of granting sufficient authority to the agent to deal with all of the property, assets, and financial affairs of the principal. A durable power of attorney can grant the agent the power to deal with property, such as a vacation home, that is located outside the state where the power was drafted. Whether the principal should permit the agent to make gifts is a contentious issue. Certainly, gifts of limited value, such as birthday gifts, pose no problem, but giving the agent the power to make gifts of substantial sums of money is more problematical. Still, many principals do grant the agent the power to make unlimited gifts in order to facilitate estate planning objectives. To protect the principal, the agent may be required to get the approval of another party before making a gift costing more than a specified dollar amount.

When Does the Power of Attorney Become Effective?

A durable power of attorney can become effective when signed or only when the principal becomes mentally incapacitated. The latter is commonly referred to as a *springing* power of attorney. A power of attorney that takes effect when signed is preferable because springing powers pose the problem of determining when the principal is incapacitated enough to trigger the power, as well as convincing third parties, such as a bank, that the principal is indeed incapacitated, thus making the agent empowered to act. If the durable power of attorney requires a physician to determine whether the principal is incapacitated, that attestation can be costly, time consuming, and can require the cooperation of the principal. For example, if the principal refuses to submit to a physician's examination, the power would apparently never come into play. The difficulties with springing powers have led most planners to favor durable powers of attorney that take effect immediately.

The perceived drawback of an immediately effective power of attorney is that the agent may attempt to use the power while the principal still has capacity. If the principal fears that the agent may use the power prematurely, the question arises as to why the principal selected an agent that he or she mistrusts. The answer is to select a more trustworthy agent. Often, the principal leaves all signed copies of the power with the attorney, with instructions to release them to the agent at the appropriate time. If the agent believes that the power should be used, the agent contacts the attorney, who confirms the incapacity of the principal and the need for the use of the power, and releases a copy of the power of attorney to the agent. This plan has the advantage of not requiring any formal *trigger* of the power, but instead relies on the good sense of the attorney.

Surrogate Decision Making for Health Care

End-of-life decision making, or, as it is often referred to, the right to die, is part of the larger right of a person to control his or her health care treatment. The right of competent persons to make decisions about approving or continuing health care treatment is well settled. A competent person has a fundamental right to control his or her medical care, even if that means choosing not to accept or to terminate life-sustaining treatment (Meisel and Ceminara 2004). The common law doctrine of *informed consent* holds that the patient has an absolute right to decide the

manner of his or her medical care, or, as famously put, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body" (Schloendorff v. Society of New York Hospital 1914).

Competency to decide on medical treatment options requires sufficient mental capacity to understand the nature and probable consequences of the decision (Restatement [Second] of Torts § 892A[2] [1979]). The patient must be adequately informed and able to understand the costs, benefits, and alternatives of proposed medical treatment. Whether the patient has the necessary capacity to give informed consent depends on the facts. A diagnosis of dementia does not necessarily mean that the individual does not have the capacity to give consent. Even a person under a guardianship may have the capacity to make a particular medical treatment decision, though in most circumstances the guardian of the person has the sole authority to make decisions on behalf of the ward.

If a patient is not under a guardianship, the physician is the most likely person to raise the issue of whether the patient has sufficient capacity to give informed consent to medical treatment; a physician can face legal liability for undertaking medical treatment of an incapacitated patient who has not given and cannot give informed consent. Unless the patient understands the nature of the illness, the proposed course of treatment, and the pros and cons of such treatment, the patient cannot consent. A physician who determines that a patient lacks the capacity to give consent has two alternatives. One is for someone to file for a guardian for the patient with the petition expressly stating that the guardian is sought for purposes of making health care decisions. Usually, guardianship is not sought because it is time consuming and costly. Instead the physician typically turns to the patient's spouse or, if there is none, to adult children or other relatives, and consults with that person as to what treatment is appropriate. Courts normally support a physician's determination of incapacity and the use of next of kin to make health care decisions. For example, California statutorily permits physicians of nursing home residents to decide that the patient lacks capacity and then, if there is no other surrogate, grants the next of kin the authority to make health care decisions (Cal. Health and Safety Code § 1418.8[a] and [c] [2008]).

Statutorily Designated Surrogate Decision Maker

Although, in practice, the spouse or family members often informally act as proxy health care decision makers for an incapacitated patient, many states have enacted laws that designate who has the legal authority to make such decisions. Known as surrogate decision making statutes, these laws exist to avoid the need to seek a guardianship when an incapacitated patient has not formally appointed a surrogate decision maker by means of an advance health care directive (e.g., appointing an agent for health care under a durable power of attorney) (Werth 2007). Most of the state laws are modeled after provisions in one of two uniform laws: the Uniform Model Health-Care Consent Act and the Uniform Health-Care Decisions Act. In the absence of a guardian or someone named by the patient, the state laws essentially impose a surrogate, or proxy, decision maker who is empowered to make health care decisions for the incompetent patient. These statutes take effect in some states if the patient is merely incapacitated or unable to communicate. Other states require both that the patient be incapacitated and in a terminal condition or be permanently unconscious. A third approach, used in Oregon, requires the patient to be incapacitated and have severe dementia.

The surrogate statutes list, in descending order, the people who are empowered to speak on behalf of the patient without any need to resort to a court. The statutes begin with the spouse, then list adult children or grandchildren, then adult siblings. Also on the list in varying order are guardians of the person, caregivers, the other nearest relative, close friends, and anyone else with a personal relationship and concern for the patient. If there is no one to act as surrogate, a few states permit the physician, often in consultation with a hospital ethics committee, to discontinue life-sustaining health care treatments.

State statutes provide varying degrees of authority to the surrogate. Most give the surrogate the authority to make all health care decisions for the patient. Other statutes limit the surrogate's authority in a variety of ways, such as limiting the right to terminate or refuse life-sustaining treatment or limit the patients for whom a surrogate can make decisions; however, it is unclear if the statutory limitations are observed in practice.

The surrogate must follow any instructions or desires of the patient. Florida law, for example, requires the surrogate to withhold or withdraw life-sustaining treatment only if there is clear and convincing evidence that the choice would have been made by the patient. If there is no indication of what the patient would have chosen, the surrogate is to make a decision that promotes the best interests of the patient. A few statutes require only that the surrogate act in good faith.

If the patient has clearly articulated a treatment preference, the surrogate must follow it. If there is no clear and convincing evidence of what the patient would have

wanted, the surrogate is required to seek out and act on evidence of what the patient apparently would have wanted. This is known as *substituted judgment*. If there is no knowledge of what the patient would have wanted, the alternative is to presume the patient to be a rational individual who would approve of care that was in his or her best interests. Although most state surrogacy statutes give priority to the patient's wishes, if those wishes are unknown, the surrogate is expected to act based on the patient's best interests. The surrogate is, in effect, bound by a descending order of priority. First, follow the explicit medical care instructions of the patient. Next, carry out the implicit requests of the patient. If the surrogate is not aware of any implicit or explicit patient desires, then the surrogate must act in accordance with the patient's values, as expressed in statements or by the patient's lifestyle. If the surrogate has no knowledge of the patient's values, then he or she must act in the best interests of the patient. Finally, some statutes permit the surrogate to act in "good faith" in the absence of evidence of the patient's attitudes.

Advance Health Care Directives

Rather than relying on a guardian or a statutorily empowered surrogate, individuals can control their health care, even if cognitively incapacitated, by signing a living will or an advance health care directive (also known as a durable power of attorney for health care.)

A living will is a signed declaration that states how a person wants to be treated in case he or she is later mentally incapacitated and terminally ill, or in a permanent vegetative state. The living will instructs the physician in general terms about how to treat the patient, with an emphasis on when to terminate life-sustaining medical treatment. Because the living will usually requests termination of life-sustaining treatment, state laws mandate that it be executed according to strict formal requirements, which typically include that it be in writing, signed, dated, and have two witnesses. Notarization, though generally not required, is the norm. The majority of state living will statutes contain a model form, which in some states is a mandatory document. Nursing home residents who execute a living will may be required to have specially designated witnesses.

Given the varying state procedural requirements and substantive mandates (see below), it is quite possible that a living will that is valid in one state will not be valid in another. Individuals who regularly reside in two states, such as retirees who have winter and summer residences, should execute two living wills—one that is valid in each state.

A living will only becomes effective upon the incapacity of the declarant, and in many states the declarant must either be in a terminal condition or be permanently unconscious for the living will to take effect. Unfortunately, an incapacitated individual with dementia is neither terminally ill nor in a permanent unconscious state; therefore, a living will, which requests the end of life-sustaining treatment, including termination of artificial nutrition and hydration, might never be honored.

Living wills can be revoked by physical destruction of the document, revocation by a later-dated living will, written revocation, and even verbal revocation. The revocation becomes effective when the physician is so notified. Some statutes permit revocation even if the declarant is mentally incompetent. Thus, the declaration by a demented individual that she does not want her living will honored effectively revokes it, even if it appears the revocation arises out of dementia rather than reason.

In addition, living wills do not help an individual who has lost mental capacity but whose medical care does not raise life or death questions. For example, if an individual is mentally incapacitated and is diagnosed with a cancer that can treated by surgery, chemotherapy, or radiation, someone needs to select a course of treatment. In this case, the patient lacks the mental capacity to make the choice, and the living will is neither operative (the patient is not terminally ill) nor does it state anything about the choice that must be made. What the patient needs in these circumstances is a surrogate decision maker who can discuss options with the physician and decide on an appropriate course of treatment. A living will does not perform that function (Meisel and Ceminara 2004).

Fortunately, every state provides individuals with the right to name a surrogate decision maker by signing a health care directive, also known as a *health care power of attorney*. Unlike a living will, which is an attempt by the declarant to manage his or her health care after the loss of mental capacity, a health care power of attorney represents the declarant's identification and appointment of another individual or individuals who are empowered to make medical treatment decisions for the incapacitated declarant.

The procedural requirements for appointing a surrogate health care decision maker depend on the state statute. Most statutes require the principal be an adult or an emancipated minor with sufficient mental capacity to understand the nature and consequences of signing the document. The degree of capacity required is lower than what is needed to sign a contract, and even an individual under a guardianship may have the required capacity. Many stat-

utes have a statutory form whose use facilities acceptance and understanding of the document, and most require a health care power of attorney to be witnessed, usually by two persons. Many statutes limit who can be a witness, for example, requiring that they not be related to the principal or be heirs to the principal's estate. Not all statutes require notarization, but most attorneys have the signatures notarized as a matter of course (Frolik and Radford 2006).

The surrogate has no authority to act until the principal has lost mental capacity, but it may not be obvious exactly when a principal lacks the mental capacity to make health care decisions. The path from mental capacity to incapacity is not always swift or steady. Individuals may gradually lose mental capacity or lose it in fits and starts. Under these conditions, the point at which the surrogate is empowered to make the decisions is unclear.

In practice, the problem resolves itself because the attending physician decides. When the physician believes that the patient cannot give informed consent, the doctor will turn to the surrogate to help make health care decisions for the principal. Together, the physician and the surrogate chart a path of medical treatment that reflects the wishes of the patient (Beinstock 2007).

Unless state law affirms otherwise, as maintained by one state statute, the surrogate can be designated to "…make health care decisions on behalf of the declarant to the same extent that the declarant could make the decision…." (Minn. Stat. Ann. § 145B.07 [2008]). Unless the principal has some compelling reason to limit the authority of the surrogate, the document should contain language as broad as the quoted statutory language. A principal may want to provide advisory language to help guide the surrogate. If there is a particular procedure that the principal does not want performed, such as a blood transfusion, the document should so state. Otherwise, because it is impossible to anticipate what medical conditions the surrogate may be faced with, the broadest authority possible should be given to the surrogate, who will then have the flexibility to make decisions that reflect the individual values of the patient (Werth 2007).

The power should specifically address the authority of the surrogate to terminate life-sustaining treatment, including withholding nutrition and hydration. State laws do place a few absolute prohibitions on the surrogate who, for example, cannot accede to or engage in euthanasia—that would be considered a homicide.

If an individual has a guardian of the person appointed, the guardian may be able to overrule a health care surrogate. Some states permit the guardian to revoke a power of attorney, but others require prior court approval. If an incapacitated individual has two different persons acting as surrogate and guardian of the person, something has gone wrong. If the surrogate was first in place and then a guardian was sought, it probably means that someone close to the principal, such as a child, objects to the decisions of the surrogate or expects to object to future decisions. In other instances, a guardian may have been appointed before the surrogate had authority to act or before there was any medical decision to be made that necessitated a surrogate. If the surrogate was not named guardian, it is often because of family disharmony that led the court to appoint someone other than the surrogate as guardian.

An individual with a progressive dementing illness should also consider signing a Do Not Resuscitate (DNR) order to avoid administration of cardiopulmonary resuscitation (CPR) such as chest compression, use of a defibrillator or intracardiac medications, artificial airways, and mechanical ventilation. Frequently, the application of CPR prevents death for only a few days; or worse, it saves the individual's life, but only after the individual has suffered additional hypoxia, and so survives in an unconscious state or with severely diminished mental capacity (Meisel and Ceminara 2004).

To prevent the use of CPR, DNR orders are issued. To ensure the legality and enforcement of DNRs, many states have enacted statutes that authorize the creation of DNR orders, describe who can make such an order, when the order is effective, and when it may be ignored.

There is no DNR statute. There are only state statutes that differ in many ways. What is common among the statutes is the aim to regularize DNR orders and their use. New York permits a DNR if resuscitation would impose an extraordinary burden on the patient (N.Y. Pub. Health Law § 2965[3][c] [2008]). The Georgia statute states that the DNR order is effective if the application of CPR would be futile (Ga. Code Ann. § 31–39–2[4] [2008]).

A DNR must be in writing, signed by the patient, usually witnessed and affirmed by the attending physician, and made part of the patient's medical record. The DNR order is, in effect, a physician's order, consented to by the patient, regarding how the patient should be treated: do not resuscitate if the physician is not present to direct the patient's care. Much of the demand for DNR orders arises from a desire to prevent emergency rescue medical personnel from employing CPR, because the provision of emergency medical treatment does not require the consent of the patient. Still, an individual can refuse emergency medical treatment, even in advance, by the use of a DNR order, if the DNR specifically states that the patient desires that no CPR be used in the event of an emergency. To make known the existence of their DNR orders, some persons wear a state law–authorized bracelet or necklace that medical personnel are required to obey (Meisel and Ceminara 2004).

Driving

It is usually not a good idea for individuals with dementia to drive. Unfortunately, state driver's license laws make it an all-too-common occurrence. Because the federal government plays no role in determining who is permitted to have a driver's license, state laws determine who can obtain a license and, more relevant to the elderly, who can retain it.

There is no uniformity among states regarding the retention or renewability of driver's licenses by older drivers. About one-quarter of the states mandate that older drivers (with the definition of "older" varying from age 65 to 75 years) must renew their licenses with more frequency. The shorter interval for license renewal presumably reflects the belief that, as individuals enter old age, they may be less capable drivers. Other states change the renewal method for older license holders by requiring that the renewal be done in person or by changing the type of testing required, such as imposing an eye examination or a test of the rules of the road. Although such testing may identify drivers with dementia as not being capable of driving safely, testing only occurs when the license is up for renewal. Up to that point, even an individual with severe dementia could have a valid driver's license and continue to drive legally. Some tests, such as vision testing, do not necessarily identity a driver with dementia. No state mandates that the elderly take a mental competency test, though some permit the state examiner to require the renewal applicant to see a physician. Other states require a mental health examination if notified by a doctor, police officer, or relative of the renewal applicant that the applicant has dementia. In all states, a renewal applicant can be required to take a mental examination if the examiner believes the person is mentally unable to safely operate an automobile (Rosenfield 2004).

Of course, none of these procedures removes unsafe drivers from the road until they attempt to renew their licenses, and, even then, they may lose their licenses only if identified as having a mental problem. More than 40 states have established Medical Advisory Boards composed of physicians to help the state licensing agency identify the kinds of disorders, such as dementia, that affect the ability to drive. A minority of states have physician reporting laws that require doctors to report potentially unsafe drivers to the licensing authority, and evidence of a cognitive disorder such as Alzheimer disease could trigger reporting (Tripodis 1997).

Absent a report being filed with the licensing agency—and even that does not guarantee a loss of license—getting a driver with dementia out of the driver's seat is left to spouses, families, and friends.

KEY POINTS

- Progressive cognitive disorders lead to the loss of mental capacity, which can result in the loss of ability to make legally enforceable decisions.
- The legal response to mental incapacity is to appoint a guardian to make decisions for the incapacitated individual.
- Various levels of mental capacity are necessary for the different kinds of decisions an individual must make to care for him- or herself.
- Guardianship is under the supervision of courts, which decide who needs a guardian; the courts can also appoint the guardian.
- Guardians are expected to act in the best interests of the incapacitated person.
- In lieu of guardianship, an individual can appoint a surrogate decision maker by creating a durable power of attorney.
- An individual can control his or her health care decisions even after the onset of mental incapacity, either by signing a living will or appointing a surrogate health care decision maker.
- The right to drive is controlled by states whose laws vary considerably in monitoring the ability of older persons to safely drive an automobile.

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CHAPTER 22

Ethical Issues and Patterns of Practice

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The complexity that surrounds dementia is vast. This is no less true of ethical issues than it is of the scientific, clinical, social, or legal issues regarding dementia. The ethical issues in dementia care, however, in comparison with many other issues in health care ethics, have a peculiar depth because of the implications of dementia for the patient and, in particular, for the person's self. Because of the fundamental importance of personhood, ethical issues resonate throughout all the fields of interest that surround dementia. Our scientific understanding of the brain and its pathology has implications for the self; manipulations of the brain (cognitive enhancement, for instance), therefore, carry ethical weight. Meanwhile, social and legal considerations can hardly avoid being relevant to ethics. And it is almost a truism to say that all clinical decisions turn out to be ethical decisions at one and the same time.

It would be convenient, therefore, if there were a model of ethics that we could take from the shelf to unpack and consider the many and various ethical issues that we must face. But to pretend that such a model or theory exists would be dishonest. For one thing, there are just too many ethical theories (see, for example, Table 22–1). For another, ethicists are constantly squabbling about which theory is the best, so it would be disingenuous to suggest that theory X is the theory to use.

I suggest that our thoughts about the ethical issues that surround people with dementia can be usefully guided by the notion of patterns of practice. Indeed, I wish to suggest that when we look for justifications in ethical discourse, we should look in the direction of patterns of practice. In the rest of this introductory section, I shall say something in general terms about ethics and the problems with (what might be called) standard approaches. This will lead me to discuss in more detail the notion of patterns of practice, which can, in any case, incorporate some of the standard approaches. I have already hinted at the importance of personhood. In the next section, I shall discuss personhood and its implications for a number of ethical issues in dementia. I will consider some of the many ethical issues that emerge in relation to dementia, with a focus on the role that patterns of practice play in structuring our thoughts and enhancing our perceptions.

Understanding Ethics

One way to think about ethics is to see the subject as a matter of argument. Indeed, clarity and coherence of argument are vital. Thus, if someone argues that there is no point in giving an acetylcholinesterase inhibitor to a person with de-

TABLE 22–1. Theories and approaches to health care ethics

The four principles approach (autonomy, beneficence, nonmaleficence, and justice), sometimes called *principalism* (Chapter 1)
Liberalism and communitarianism (Chapter 5)
Casuistry (Chapter 7)
Utilitarianism (Chapter 8)
Deontology (Chapter 9)
Kantian ethics (Chapter 10)
Feminist approaches (Chapter 11)
Virtue theory (Chapter 12)
Moral relativism (Chapter 13)
Religious approaches (Chapters 14–19)
Narrative ethics (Chapter 20)
Hermeneutic ethics (Chapter 28)
Conscience (Chapter 46)

Note. For further details on all of the theories and approaches that appear in this table, the reader should see the definitive text, Ashcroft et al. (2007); the chapter numbers in brackets refer to the chapters in that work, which mainly cover the topic concerned.

mentia who is in a nursing home, it is perfectly sensible to push for the premises of this argument. The premise might involve the presumed severity of the dementia and, therefore, it might reflect a belief about the efficacy of the drugs for people in the more severe stages. This premise might be linked to a belief that there are better ways to improve the quality of a person's life at this stage than by using antidementia drugs; for instance, by paying attention to the psychosocial environment. An alternative premise might be entirely economic: that the drugs are only cost-effective inasmuch as they keep people out of institutional care. Seeking the premises of the argument helps us to decide in a more informed way whether the argument makes sense. This is a type of ethical analysis, because it allows us to seek to understand whether it is right or wrong to give these drugs under designated circumstances.

In the case I have chosen, the premises have a factual basis: there may be evidence pertinent to whether something is right or wrong. But it could be that the premise is more obviously about values—there could be covert ageism at work. Perhaps the underlying premise is that older people with dementia are not worth extra funds, especially when they are in the more severe stages of the condition. Laying out the argument so that its commitments (in the form of its premises) can be seen clearly has much to commend it.

Furthermore, there must be coherence in the logic of the argument. For instance, if the reason for going to war (*Q*) is that a country has weapons of mass destruction (*P*), and yet it does not have weapons of mass destruction (*not-P*), then *P* cannot be the reason for going to war (because both *P* and *not-P* cannot be simultaneously true). In formal terms, the argument would run like this: if *P,* then *Q;* but *not-P,* therefore *not-Q.* This sort of logic underlies some of the arguments we shall consider in this chapter. For instance, if people with severe dementia and dysphagia are suffering hunger, it might be argued they should be artificially fed. But if, in fact, they do not suffer hunger, there is no need for artificial feeding. Just as there may be reasons other than weapons of mass destruction to start a war, so there may be other reasons to feed someone artificially. But these reasons need to be set out clearly, and we shall also be interested in the evidence that supports the reasons. Furthermore, although the reasons are supported by facts, it can readily be appreciated that the facts are often value-laden. This must also be perceived with clarity, because the issues are not trivial. As is the case in war, lives are at stake.

Clear argument is important, but some arguments are more important than others, and sometimes medical ethicists seem to relish the argument more than the content. At a deeper level, it is the content of the argument that is all-important. For clinicians, as opposed to theoreticians, the questions are typically "What ought I to do?" or "Is the decision I am making moral or immoral?" The personal and imperative nature of these questions means that many of the standard approaches in medical ethics seem either partially or sometimes completely irrelevant.

Standard Approaches

Standard approaches to medical ethics include utilitarianism, deontology, and principlism. Utilitarianism is a form of consequentialism, which states (in various forms) that the right action is the one that maximizes happiness or pleasure. The consequences of the act are the keys to its rightness or wrongness. This led to the idea that there might be a felicific calculus by which moral judgments are made. It is important to see that, having made the calculation, presuming that of two options one maximizes pleasure and the other does not, the conclusion is that the maximizing option is the right thing to do. If one option involves killing one person and another involves killing several, other things being equal, the right thing to do is to kill the one person.

Deontology, on the other hand, considers duties to be more important than consequences. Some have held, for

instance, that there is a duty to tell the truth, even if someone might thereby be hurt. Such duties can be derived from moral rules or principles and reflect basic rational principles. For instance, it is rational to treat other people as one would wish to be treated. This can be used to formulate a duty to care for others who are less fortunate. Nevertheless, it also means that, having made a promise, the promise must be kept as a matter of duty. Ordinarily, we would accept that this is the case. But one might ask whether it is always the case that duties—in this rather absolute sense—must be regarded as defining the right thing to do.

Finally, the four principles approach (Beauchamp and Childress 2001), derived in part from utilitarian and deontological roots, and enormously influential in medical ethics, suggests that, in discussing moral dilemmas, the principles of autonomy, beneficence, nonmaleficence, and justice should be used to help decide the right thing to do. There is no doubt that these principles do give us a vocabulary for ethical discourse and they are, by and large, the important principles in health care. Autonomy is generally given priority. And yet, the four principles do not in themselves provide a means to decide between them if there is a clash. What if beneficence suggests that the patient should be treated, but the advance directive, which expresses the person's previous autonomous wishes, declines treatment for what turns out to be a treatable condition?

In *standard* cases the standard approaches will provide quick answers. The consequences of not treating a suicidal patient with a psychotic depression seem, on the whole, to justify compulsory treatment on utilitarian grounds. In deontological mode, we have a duty to inform patients of the diagnosis of dementia if they wish to be told. If a woman with a mild dementia still has the capacity to refuse a particular treatment, her wishes should be respected on the grounds of autonomy. However, we only need to add a little complexity and things become less straightforward.

For instance, in discussing utilitarianism above, I ended by saying that the right thing to do was to kill the one person rather than the many. But one might reasonably object that it is *never* right to kill another innocent human being. Looking at the outcome, or the consequences, as if this provides such a definite answer as to leave no room for doubt, might seem callous. It overlooks the fact that most of us would find any killing of someone else repugnant and against our basic instincts. We might, accordingly, wish to argue that some attention needs to be paid to what we *become* by what we do. In other words, we might wish to focus on the agent, not solely on the outcome. The underlying question is: what is it to live well as a good human being?

This is the sort of question addressed by virtue ethics. The answer to the underlying question is that the virtues tell us how to live. Because virtue theory goes back as far as Aristotle, it is odd not to refer to it as a standard approach. But for many years it seemingly disappeared from view. There has been a renaissance (Anscombe 1958/1981), but virtue ethics remains somewhat marginal. Its importance is that it reminds us that it is not just *what* we do that matters, but *how* we do it. This is put perfectly by Hursthouse (1999):

> Although I am, personally, sympathetic to doctors rather than otherwise, one does hear occasional hair-raising stories about the arrogance and callousness of some. What people often complain about is not whatever decision the doctors made, but the manner in which they delivered it or acted on it. No expressions of regret, no expression of concern over whether anything could be done to make it less likely that such decisions would have to be made in the future; having made (what they take to be) the morally right decision, they seem to think that they can review their own conduct with complete satisfaction. But if someone dies, or suffers, or undergoes frightful humiliation as a result of their decision, even supposing it is unquestionably correct, surely regret is called for. A dose of virtue ethics might make them concentrate more on how they should respond, rather than resting content with the thought that they have made the right decision. (p. 48)

Or, take the deontological example of keeping promises. Sure enough, we ordinarily wish to keep promises. Children who have promised their mother, when she was well, not to put her in a home, find themselves in a terrible dilemma when she then develops dementia and starts to wander in the streets at night only partially clothed. There is no simple way out afforded by appeal to any particular duty. They will have to make judgments based upon their broad appreciation of the situation. A way forward might be achieved by looking at their mother's life as a narrative. In that case, her life as a whole needs to be considered: would she have wished to be seen in an undignified state in the street? How does her narrative interact with those of her children? What were the circumstances under which her children made the promise, and have things now changed significantly? The narrative has changed. The narrative approach, which takes account of history, allows a more nuanced discussion than seems possible in the face of clashing duties. It also allows that the decision may or may not remain difficult for all concerned, but there is certainly no pretense that things will be easy.

Finally, the principle of autonomy, with its emphasis on the rights of the individual to self-determination, will always be consequential in connection with people who have impaired decision-making abilities. But where does this get us when we are faced by the realities of long-term care? We are then faced with a situation in which the per-

son with dementia is inevitably dependent on others. This line of thought has been pursued by Agich (2003), who suggests that the concept of autonomy, properly understood, requires that individuals be seen in essential interrelationship with others and the world. He sketches, in a convincing way, the extent to which our sense of autonomy is often predicated on our relationships:

> Autonomy fundamentally importantly involves the way individuals live their lives; it is found in the nooks and crannies of everyday experience; it is found in the way that individuals interact and not exclusively in the idealized paradigm of choice or decision making that dominates ethical analysis. (Agich 2003, p. 165)

Relationship and dependency, along with elements from narrative and virtue ethics, are linked to the feminist approach to health care ethics, which—instead of rights, autonomy, and justice—has tended to stress interrelationships, responsibilities, and the nature of caring (Gilligan 1982; Noddings 1984).

In the concrete circumstances of everyday life, therefore, the answer to the question "What is wrong with the standard approaches?" is that they fail to engage with the real subtleties that emerge when we think about what we become by our decisions, our lives as a whole, our interrelating narratives, and the nature of our caring relationships (Hughes and Baldwin 2006). These other approaches not only convey the complexity in a more realistic way, but they inform real discussion of ethical issues.

Baumrucker (2005), for example, presents a case study of Mrs. J, a woman with dementia for whom a decision has to be made concerning continuation of renal dialysis. There is a degree of conflict in views between the physician in charge of the nursing home where Mrs. J lives and Mrs. J's daughter. The case is commented on by a physician, who summarizes many of the relevant medical facts surrounding the case. The principles of medical ethics, such as autonomy, are certainly considered. But in the final sentence, in what seems to be a summing up of the right way forward, the physician says: "A compassionate discussion with the daughter…would help build consensus in the plan of care…" (p. 387). The lawyer who discusses the case talks about the need for all parties to understand the situation better. The ethicist, who favors stopping treatment, comments: "The daughter should be given ample compassion and support…" (p. 390). The nurse suggests: "The communication between them needs to be forthright and truthful" (p. 391).

What emerges is not a simple recommendation dropping from the felicific calculus; neither is it a clearly prescribed duty or an overriding principle. Instead, the experts commend compassion, dialogue, shared understanding, and interrelationships of support, forthrightness, and honesty. In a somewhat messy fashion, we find elements of virtue theory and the feminist approach. The narratives of all concerned are prominent, as is the idea that right communication (truthful, compassionate, etc.) will lead to the best outcome. This has sometimes been called communicative ethics (Moody 1992) and is yet another version of a nonstandard approach to ethical decision making.

The tricky aspect of discussing ethical issues is to weave these threads together, to present an approach that seems coherent within itself, but which also coheres with the reality of clinical practice. The notion of patterns of practice serves just this purpose.

Patterns of Practice

Our lives are densely patterned. Our ways of talking, thinking, working, playing, loving, fighting, debating, arguing, building, creating, perceiving, teaching, and learning are all patterned. Language itself requires patterns of practice to convey meaning. Health care is carried out according to certain practices: a medical practitioner is someone who practices in certain ways, and professional practice is conducted in accordance with regulated rules or customs. Part of qualifying as a doctor or other health care professional is adopting a particular pattern of practice. Hence, we can think of clinical practice as being carried out in accordance with certain patterns. Of course, clinical practice involves many things: various kinds of knowledge (from anatomical to legal) and a great variety of skills and competencies that are attitudinal, practical, and psychosocial. And it is, by nature, ethical too; in other words, clinical practice cannot escape its ethical commitments. So what contributes to the patterns that constitute ethical clinical practice?

We have already mentioned the idea of rules that govern professional conduct. In addition, there are broader social, economic, and political structures or forces that govern how health care professionals behave; they shape patterns of practice in overt and covert ways. One overt method in which patterns of practice are shaped is by the need to ration health care in certain ways. In addition to these overt economic and political pressures on patterns of practice, there can also be social pressures. For instance, patterns of practice regarding the disclosure of a diagnosis such as cancer can vary in different cultures (Akabayashi et al. 1999). There will also be differences within cultures. In dementia care we see a significant variety of attitudes toward disclosure of diagnosis, even among professionals

with a similar sociocultural background (Bamford et al. 2004). These differences reflect the varying emphases placed on principles, such as respect for autonomy and the need for beneficence. More than this, however, patterns of practice will be influenced by a whole raft of ethical theories and moral attitudes. For instance, intuition and conscience have a role in shaping patterns of practice. Similarly, in practice, people tend to be concerned about the possible consequences of their actions while, at the same time, they feel a duty to behave in specific ways. Hence, people put into practice a variety of principles, which in turn reflect an array of values. If patterns of practice can be thought of in terms of practitioners navigating through moral space, we might say that how a person finds his or her way will inevitably reflect inner dispositions. Put more simply, ethical patterns of practice inevitably incorporate the values.

All of this is summed up in Figure 22–1. One might wonder how, when we look for justifications in ethical discourse, the notion of patterns of practice can help. It might seem as if we should go back to the most appropriate underlying moral theories or approaches. The difficulty with going back to basic moral theories is that this tends to perpetuate squabbles among consequentialists, deontologists, principalists, and the like. There is at least the hope that an appeal to patterns of practice might circumvent such wrangles.

There are two points to note. First, patterns of practice incorporate or reflect the various ethical principles and attitudes that we imbibe in the course of our moral education. Second, therefore, the theoretical debates are worked out (in a practical way) in our patterns of practice. Therefore, it could be argued, the crucial factor for determining that the right ethical decision is made is *phronesis*, or practical wisdom. Indeed, the importance of practical wisdom in dealing with the behavioral problems in dementia has been recognized:

> This type of wisdom includes a certain attitude, a certain condition, obtained by practice. Virtues are based on education and training; they are acquired in the process of acting and living. Virtues grow from experience. …Understanding dementia is in the end a practical matter, a matter of being experienced. (Widdershoven and Widdershoven-Heerding 2003, p. 110)

Another factor in favor of using the notion of patterns of practice in ethical decision making is that it *feels* right. When faced by a difficult clinical decision, for instance, concerning whether or not a person with cognitive impairment should be stopped from driving, the clinician will fall back on patterns of practice rather than go back to basic principles in medical ethics. This may involve, for example, recommending a specialized assessment of driving. Of course, the decision to make such a recommendation reflects many ethical considerations. But once this course of action has become ingrained within the clinician's patterned behavior, through the education and experience referred to above, no further specifically ethical ratiocination needs to occur. The ethical justification is supplied by the pattern of practice.

It could be argued that, although patterns of practice provide a heuristic device in discussions of ethical decision making where things go smoothly, the notion will be no more useful than the basic principles when ethical decisions get tough. The answer to this is to acknowledge that ethical deliberations cannot be blind to the underlying principles and theories derived from moral philosophy. However, there is a way in which patterns of practice might themselves provide moral solutions. Indeed, these practices must cohere with the multifarious practices that otherwise pattern the lives of human beings (Hughes 2006b). Using the notion of patterns of practice helps to shift attention away from theories to the practical working out of ethical dilemmas in the real world (Hughes and Baldwin 2006). The next section considers the notion of personhood and its importance, since this underlies many of our patterns of practice.

Understanding the Person With Dementia

The Importance of Personhood

Kitwood and Bredin (1992) first stressed the importance of person-centered dementia care (see also Brooker 2004). Kitwood placed a special emphasis on the *person* with dementia, as opposed to the person with *dementia*. He defined personhood as "a standing or status that is bestowed upon one human being, by others, in the context of relationship and social being" (Kitwood 1997, p. 8).

The importance of personhood stems from the way in which it defines us as the creatures we are. It confers on us our standing as individuals worthy of respect. The reason we should be treated with dignity originates in our status as persons. The idea, however, that personhood is "bestowed" (as Kitwood suggests) or "conferred" (as I have just suggested) is perhaps misleading. It could be argued that our personhood, and the ethical status it confers or bestows, is inherent: this is simply what it is to be a human being in the world.

Some philosophers define personhood in terms of consciousness and, in particular, in terms of memory (Locke 1690; Parfit 1984). The upshot of this is the implication that personhood is lost in dementia. If I cannot in-

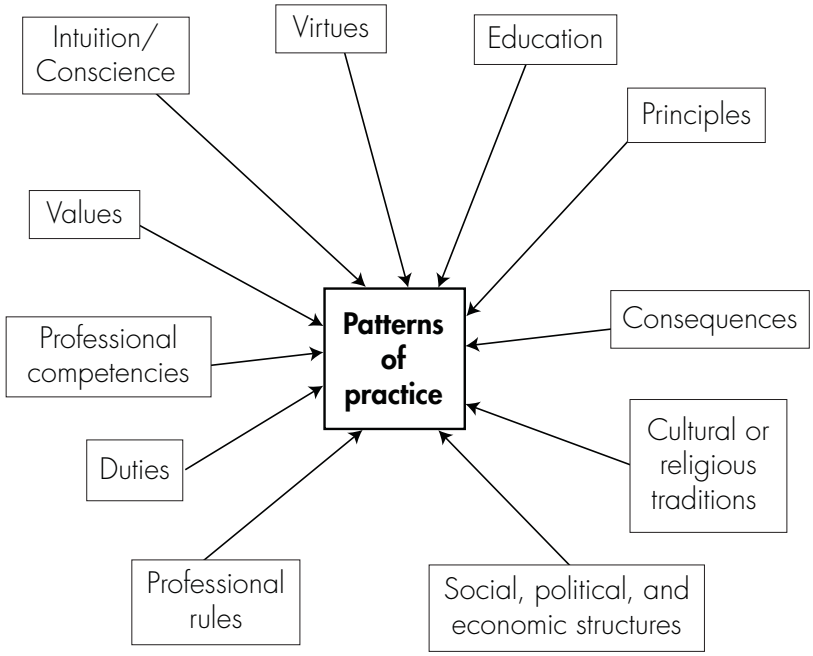

FIGURE 22–1. The makeup of patterns of practice.

tegrate myself by remembering, it is argued, I cannot preserve my personal identity. If, however, I am not the same person I once was, then something done before (such as *my* advance directive) will not relate to the person I am now (Hope 1994). Moreover, if advanced dementia means that the person no longer exists, then the advance directive has no legitimacy (Buchanan 1988). Loss of personhood would mean a loss of basic rights that people otherwise expect. My social and legal standing and ethical status are all linked to my personhood. Thus, it seems important, for the sake of people with dementia, that personhood should be retained. We can still argue, as Buchanan (1988) did, that the individual with dementia deserves care purely on the grounds that he or she is sentient. Nevertheless, this leaves the individual denuded of what underpins our deep-seated notions of respect for human beings.

Luckily, there are strong philosophical positions to support the view that, even in severe dementia, the person persists (Lesser 2006; Matthews 2006). A broader view of personhood, regarding the person as a situated embodied agent (Hughes 2001), allows the idea that, even in severe dementia, it is still possible to point to the person's history and relationships as a way of maintaining personhood. Furthermore, the person persists through his or her bodily continuity and the links between this and his or her situated agency (Aquilina and Hughes 2006). The notion of being situated or embedded is crucial to this view. We are all situated in our physical and psychological histories, but also in a social, legal, family, ethical, and spiritual context. The number of fields in which we are situated expands in the same way that our possibilities as humans cannot ever be fully pinned down and circumscribed.

Personhood is important because it opens up the ways in which people with dementia should be regarded and treated. This broader philosophical view is not just theoretical. It carries weight in practical terms. People should not be solely regarded and respected as cognitive beings. As Post (2000) has argued, there are numerous dangers for our humanity if "hypercognitivism" (in which personhood is tightly tied to cognitive status) is allowed to go unchecked.

> The person with dementia…is part of our common humanity as an emotional and relational being and therefore must be treated with care and respect. Only a view of humanity that excludes emotion and relationality would ignore this and such a view would be both callous and inhumane. (Post 2006, pp. 232–233)

Another reason for holding to the broad view of personhood in dementia is that this philosophical position suggests practical approaches. If part of our personhood relies on our social interactions, it follows that the social environment, in numerous ways, could be benign and enhancing or malignant and destructive of even that personhood that might remain despite significant brain damage (Sabat 2001). The following statement further describes this position:

> It is in the social dynamics of everyday life beyond the neuropathological processes in their brains that people with dementia can be supported in, or experience assaults on, their personhood. (Sabat 2006, p. 298)

In a similar vein, we find demands for a more sustained attempt to encourage person-centered dementia care by pursing research involving the person's subjective experience, the interactional environment and the broader social and cultural context (O'Connor et al. 2007).

If we turn to the notion of patterns of practice we can say that our interactions with people with dementia are rarely (if ever) purely cognitive. Clinical encounters with people with dementia typically introduce legal, social, and ethical issues, to name but a few. Because we are embedded in these practices involving legal, social, and ethical encounters, it is difficult to imagine a pattern of engagement that denies these ways of being for the person with dementia. Of course, there is a possible world in which we might enter a person's room without awareness of the family photographs or the certificates on the wall relating to wartime service, in which we might even ignore the information from the caregiver as to the person's normal abilities to interact in simple ways—by smiling or by gestures—and instead we might perform a cognitive test to sum up the person's being (or nonbeing). Such a world, or pattern of practice, would not only lack humanity but would be difficult to imagine. It would not fit with our other patterns of practice in which we value family, community, and history. Our standard pattern of practice takes personhood in the broad sense (involving biological, psychological, social, and spiritual aspects) as a given. Thus, personhood is important because of the way in which it underlies many of our patterns of practice.

Quality of Life

A good example of how personhood must inform our patterns of practice is in connection with quality of life. It is obviously true that an intervention in dementia, whether it is the introduction of a new drug or some form of social support, should, in some sense, enhance quality of life. Not surprisingly, therefore, there has been a huge growth in the development of instruments to measure quality of life. However, such measurement is inherently problematic. Quality of life is a multidimensional concept with no clear or fixed boundary, and there is little agreement about what constitutes the individual domains of quality of life; about the standard for each domain that would reflect a low or high quality of life; or who determines the relevance of each domain to the individual (Bond 1999).

In addition to the problem of domains, there is also a subjective-objective problem and a then-and-now problem associated with quality of life (Hughes 2003). The subjective-objective quandary is that it is difficult to decide whether quality of life is mostly a matter of the person's inner states (e.g., of pleasure or satisfaction) or of their outer states (e.g., the degree of physical disability); and, if their inner states are important, how these might be known in severe dementia. The then-and-now problem concerns whether the standard against which a person's quality of life is judged should be based on those things the person valued in the past or those things currently valued. In the past, the person might have enjoyed intellectual debate, but now it might be that the quality is maintained by much simpler pleasures. This is no mere theoretical consideration. Take, for instance, this wife speaking of her husband:

> If you'd said to me 10 years ago at the beginning of this illness, in 10 years' time my husband will become immobile, speechless, doubly incontinent, unable to do anything for himself, and really has only got his music and nourishment and human touch as the three pleasures. He's also practically blind as well. … And if somebody said to me, 'Does somebody in that state have any quality of life?' I think 10 years ago I'd have said, 'No.' But working with him now, caring for him now, there is still quality of life; there are still things that he appreciates. He likes the feel of the sun on his hands, he likes to see what he probably distinguishes as bright colors, but what they are he has no idea. He likes his music, he likes to be sung to, he likes to be played with in a way that you play with a small child, and he loves human contact and cuddles and tickles and all these sorts of things. And yes, there is still a quality of life there. (Hughes and Baldwin 2006, pp. 100–101)

What does all of this mean with regard to measuring quality of life? It certainly entails that researchers should be cautious in their use of words: quantities do not always capture qualities. It also means that it would be better to ask people with dementia themselves to define good outcomes, rather than invent more or less valid measurements (Bond and Corner 2004). And this takes us back to personhood.

What constitutes a person's quality of life will be as broad and varied as the things that contribute to personhood. Just as personhood cannot be circumscribed—there are always additional ways in which we can potentially express ourselves as flourishing human beings—so, too, we cannot shut down (e.g., by specifying the domains of quality of life) the possible ways in which an individual might feel the quality of his or her life has been enhanced. Personhood and the possibilities of human flourishing underpin quality of life. Our patterns of practice need to reflect this reality. Therefore, if in judging a person's quality of life we were to stipulate ahead of time the ways in

which he or she should flourish—irrespective of the individual—we would thereby be acting in a way that would not cohere with our broader patterns of practice, in which we take for granted that humans express themselves and derive satisfaction in a wide variety of predictable, but also idiosyncratic, ways.

Rationing and Ageism

Another reason why there should be concerns about efforts to quantify qualities is because such quantifications can be used to make decisions, not just about individual lives, but about older people generally. The notion of a quality-adjusted life-year (QALY) is often used as the currency in calculations of cost-effectiveness. The United Kingdom's National Institute of Health and Clinical Excellence recently decided that, although acetylcholinesterase inhibitors are clinically effective, they are not cost-effective except in the moderate stage of the disease. On the basis of a QALY calculation, therefore, people with mild dementia are denied treatment by the National Health Service. This would be fair enough if it were not for the thought that QALYs might be inherently ageist (Harris 1987). The decision in the United Kingdom has led to acrimonious exchanges in the pages of the *Journal of Medical Ethics* (e.g., Claxton and Culyer 2006; Harris 2005).

Whatever the rights and wrongs of that particular argument, the basis of many such calculations has been questioned. Arnesen and Norheim (2003) doubt that one can use a hypothetical trade-off to compare the value of life lived in different health states in terms of the number of life years the respondent is willing to pay to improve those states, and argue that it is difficult to conceptualize a trade of lifetime against quality of life, because both are so deeply interrelated. Quality and quantity are different dimensions of existence that cannot be substituted for each other.

The idea that the quality and quantity of our lives are deeply interrelated is, in many ways, opposed to the scientific inclination to reduce phenomena to simple parts. One question might be whether our patterns of practice out in the world of persons—interacting, relating, and reflecting—is really a concept in which phenomena are split into components or clumped into wholes. Common sense tells us that we mostly deal with wholes, including whole people. Scientific reductionism is a perfectly valid pattern of practice, but it occupies only one part of our otherwise complex lives. It does not provide the pattern for our lives as a whole.

Having said this, it is important to recognize that maximizing health would seem to be an ethical objective (Culyer 2001). The process by which maximizing health is achieved requires some sort of societal consensus. If this were not achieved, clinicians would find themselves in a difficult position, having to act both as advocates for these patients and as stewards of scarce health care resources. Weinstein (2001) argues that a return to unconstrained use of technologies and resources will fail because of limits at the societal level. Citizens and physicians must accept the concept and consequences of resource limits, just as they accept speed limits, zoning laws, and other self-imposed constraints in the interest of the greater good.

This seems very sensible: we need a societal pattern of practice, reflected in our political institutions, which will recognize the need to distribute health care goods in an equitable manner. However, there must also be recognition that political institutions can sometimes get things wrong. Sometimes people will break laws for valid reasons (e.g., speeding in a medical emergency). This would be exceptional, but the moral possibility exists. It may be that in the United Kingdom the decision to stop the use of antidementia drugs in mild Alzheimer disease is an example of an area in which clinicians will be inclined to bend the rules in particular cases.

The worry lurking behind decisions about resources and older people is that there may be a covert ageism at work. And sometimes, ageism is not so covert:

> In each of our lives there has to come a time when we accept … that a reasonable limit has to be set on the demands we can properly make on our fellow citizens in order to keep us going a bit longer. (Williams 1997)

The statement above might sound reasonable, but what about this?

> So the values of the citizenry as a whole must override the values of a particular interest group within it. (Williams 1997)

According to this view, older people are "a particular interest group" who can be ignored on the grounds that they have had (using a baseball analogy) enough time at bat (which, in countries where cricket is played is referred to as *a fair innings*). In response to this view, Grimley Evans (1997) objected to the exclusion from treatment on the basis of a patient's age, without reference to his or her physiological condition.

Still, there are a number of ways in which a fair innings argument can be defended (Clarke 2001). For instance, it can be said that since we shall all (potentially) be old, looking at a life as a whole and taking a prudential view (spending more on an earlier phase than on the later phases), does not add up to an *-ism*. If, as an Englishman, I am racist about Scotsmen, the vicious thing is that I see myself as better or the Scot as inferior. But if, as a younger man, I judge that older men should not have so much money spent on their health care, as long as I apply the same judg-

ment to myself when I am old, I shall not have acted wrongly—only with prudence. On the other hand, others argue that the fair innings argument is necessarily based on an ageist premise because it lumps all older people together (Rivlin 2000). If there is only one intensive care bed left and an Englishman and Scotsman both need it, it should not go to the Englishman purely on the grounds that the other man is Scottish. Similarly, if a 40-year-old and a 75-year-old need the bed, it should not not go to the 40-year-old purely because the other person is over three score years and ten. It might well be that the 75-year-old is in a worse physiological state, but this need not be the case. Indeed, many older people will be inclined to give way to a younger person in such circumstances. If it were the case, however, that many Scotsmen would be inclined to give way to Englishmen, it does not follow that all Scotsmen should act in this way.

The serious point is that people must be treated as individuals. There are two ways in which the notion of patterns of practice might be useful here. First, does my pattern of practice *in fact* discriminate against people purely on the grounds of age (or race, sex, etc.)? Second, how does my pattern of practice in this regard cohere with my other patterns of practice and those of people around me?

It should also be noted that there is empirical work to support the anti-ageist stance. Older Swedish people, in general, do not want age to be used as a criterion for prioritization in health care (Werntoft et al. 2005). Older people do not wish to give up their place for cardiac surgery to younger people in the United Kingdom, although willingness to do so seems to increase with age (Bowling et al. 2002), which might be for positive or negative reasons. Yet, there is evidence that older cardiac patients are treated differently because of their age (Bond et al. 2003). There is also evidence that older people sometimes benefit more from particular investigations or treatments than younger people. For instance, in a study of colonoscopy in those age 85 years or older, there was a comparatively high yield of positive findings, with low levels of complications, suggesting that clinical need—not age—should be used as the basis for this investigation (Yoong and Heymann 2005).

Existential Concerns

As we have seen, our patterns of practice are influenced by empirical matters of fact. But they are also influenced by values, some of which touch the boundaries of our being. Karl Jaspers referred to this point as the "limit-situation" (*Grenzsituation*). Death, guilt, and suffering can bring us to the point at which human existence "founders" or is "shattered," but it is also through this experience that we can be liberated and become more fully human (see Macquarrie 1972, pp. 245–246). Thus, although the literature about the ethical challenges facing caregivers often records the anxieties and difficulties of caring, it also shows how, for some, the experience of caring enhances the caregiver's life (see Hughes et al. 2002b). Albinsson and Strang (2003) also record a host of existential concerns that affect caregivers, from feelings of guilt to anticipatory grief to an awareness of meaning. Previously, Leichtentritt and Rettig (1999) demonstrated the complexity of the moral landscape, especially in connection with passive euthanasia. Not only do a variety of considerations influence our values, but also our relationships, and the proximity of our relationships to those concerned affect our perceptions of the issues that surround passive euthanasia. Physicians need to discuss death with their patients, but they must also be aware that their own views are shaped by a variety of influences (Rurup et al. 2006).

Increasingly, the issues of active euthanasia and physician-assisted suicide are being considered. One thing is clear: it is increasingly possible and desirable to talk to people about their wishes concerning death. This will often reveal that some people wish their lives might be ended. When this occurs, studies in both Sweden (Forsell 2000) and the United States (Emanuel et al. 1996) have emphasized the importance of excluding a treatable psychiatric disorder such as depression. There is a strong correlation between the desire for death and depression. Strikingly, in a study by Emanuel et al. (1996), patients who actually experienced pain were more likely to find euthanasia or physician-assisted suicide to be unacceptable. Patients who seriously discussed euthanasia or who took steps toward suicide were significantly more likely to have depression and psychological distress. It was also notable that one in seven oncologists in this study said they had carried out euthanasia or physician-assisted suicide, despite the fact that both were illegal. I shall return to the topic of euthanasia, but for now merely wish to note that dementia—and the threat it poses to personhood, which at the limit is the threat of death—inevitably raises a host of existential concerns, but also the possibility of psychological disturbance.

For this reason, death must be discussed. Existential distress may need to be dealt with. As Rurup et al. (2006) suggested, our patterns of practice are shaped by a variety of internal and external factors, from our religious beliefs to our responsibilities as doctors, nurses, or relatives. We also have different perspectives on the person: as someone with a narrative and life history or as someone known only in the present with dementia. This complexity reflects our "situatedness" as persons in a historical and social context. But what is called for is some form of coherence in our patterned responses.

Withholding and Withdrawing Treatment

The coherence of our patterns of practice becomes of the utmost importance in decisions that might hasten death, and the importance stems from the significance of death for persons as situated embodied agents. People who are competent are able to think rationally about their treatment choices. Investigators monitoring a study with 2,073 participants who were followed over a 2-year period in the United States found that 85% who had chosen to forgo life-sustaining treatments did not change their minds (Danis et al. 1994). Overall, the population chose to forgo one more treatment after 2 years. People wanted more treatment if they had been hospitalized, had had an accident, had become immobile, depressed, or if they had lost social support. Still, people are entitled to change their minds. A United Kingdom study found that cognitive impairment increased the chances that a person would opt for life-sustaining treatment (Fazel et al. 2000). Our patterns of practice should reasonably aim to involve people in their treatment decisions. Under circumstances of cognitive decline, or where matters are emotive, it might be an almost reflex reaction for families to insist on therapy in the absence of evidence of effectiveness. The clinician, while accepting the views of all concerned, should stick to a pattern of response that contains some coherence.

For instance, pneumonia can occur in people who are not dying, for whom treatment with antibiotics might be useful. In end-of-life pneumonia, antibiotics have little effect on mortality (Janssens and Krause 2004). Some research shows no difference in mortality between those receiving antibiotics and those only receiving palliative care (Fabiszewski et al. 1990). Pneumonia causes sustained suffering for people with dementia, whether or not antibiotics are used (van der Steen et al. 2002), but antibiotics do have palliative properties (Clayton et al. 2003). The difficulty in such cases is to keep the aim clear: is it to cure or to palliate? How effective might the treatment then be? Once again, there will not only be factual matters to be decided (the province of evidence-based medicine), but also issues of value, which will often be complex and conflicting. This is the province of values-based practice (Fulford 2004). But not just any values are acceptable: there must be a fair way of revealing and acknowledging the values, and there must be coherence in how the values are weighed.

The possibility of conflicting values is evident in what Aminoff (2005) has called the "overprotection phenomenon," in which a patient wants more aggressive treatment than the clinicians think fit. In particular, sticking to a coherent pattern of practice is tested when faced by a "bad patient," one with dementia, but also with a history of having been a sexual abuser; Schonfeld et al. (2007) stated that health care must be differentiated from criminal justice. Health care providers are obligated to provide competent care to patients without regard for social or personal characteristics. It is not just that the patient's humanity demands our competent and respectful care, but that ours does.

Our humanity is also seen in our attitudes toward resuscitation. Much more careful thought needs to be given to the issue of whether it is even appropriate to have discussions with people about resuscitation (Regnard and Randall 2005), particularly in severe dementia, when the chances of a successful outcome are so low, even in a hospital (Ebell et al. 1998). Outside a hospital, the chances of cardiopulmonary resuscitation leading to survival are very poor, and the procedure of resuscitation is burdensome (Awoke et al. 1992; Conroy et al. 2006; Zweig 1997). It is in just this sort of situation that the doctrine of ordinary and extraordinary means comes into effect.

This suggests that we are morally bound to take ordinary measures to, for instance, prolong life; but we are not morally culpable if we do not take extraordinary means. Of course, it might be argued, whether something is "extraordinary" only depends on the circumstances. But according to this doctrine, something is extraordinary if its chances of success are low and if it is burdensome. This could be couched in terms of futility and the principle of nonmaleficence. However, the doctrine is better understood in connection with the concrete circumstances of clinical practice:

> Certainly there is a moral obligation to care for oneself and to allow oneself to be cared for, but this duty must take account of concrete circumstances. It needs to be determined whether the means of treatment available are objectively proportionate to the prospects for improvement. To forego extraordinary or disproportionate means is not the equivalent of suicide or euthanasia; it rather expresses acceptance of the human condition in the face of death. (John Paul II 1995, paragraph 65)

Artificial Nutrition and Hydration

What we see in this quote from a Catholic pope is reflected in writings on the use of artificial nutrition and hydration from a Jewish perspective (Gillick 2001), in which a vital distinction is made between whether the person is or is not in a condition that will ineluctably lead to death without any prospect of recovery. The evidence is lacking that tube feeding is efficacious in severe dementia (Finucane et al. 1999), so there are no good grounds for insisting that tube feeding is a moral obligation (Gillick 2000). Not only are there a number of conservative approaches and techniques that might be helpful in feeding people with severe dementia and preventing them from becoming malnourished,

but also the evidence concerning weight loss in Alzheimer disease (Gillette Guyonnet et al. 2007) and the efficacy of tube feeding in dementia continues to suggest that artificial feeding should not be the norm (Alvarez-Fernández et al. 2005; Hoffer 2006; Sanders et al. 2004). The pattern of practice that suggests everything possible should be done to save life is laudable, but if used to press for ineffective and burdensome treatments, it conflicts with supporting a pattern of practice that encourages a realistic acceptance of the concrete circumstances of our lives.

Back to the Person

The lives of people with dementia and their caregivers are patterned by practices. In the best world these patterns will be enhancing; they will recognize the variety of ways in which quality of life can be maintained; they will guard against discrimination against "the elderly" as if they lacked individuality; they will enable spiritual and existential concerns to be expressed; they will honor life, but accept the reality and inevitability of death. These are the ingredients—along with symptom control—of palliative care, toward which Kitwood (1997) was moving. The need for a hospice type of approach for people with dementia is increasingly recognized (Hughes 2006a; Post 2000; Volicer and Hurley 1998; and see Chapter 19, "Management of Advanced Dementia"). The key is the possibility of meaning, which can be enhanced and maintained by others, and which is not purely a matter of rational communication, but is also emotional and relational:

> The reality is that until the very advanced and terminal stage of dementia, the person with dementia will usually have sporadically articulated memories of deeply meaningful events and relationships…Even in the advanced stage of dementia… one finds varying degrees of emotional and relational expression, remnants of personality, and even meaningful nonverbal communication (as in the reaching out for a hug)…there is an emotional and relational reality in the lives of the deeply forgetful. (Post 2006, pp. 231–232)

People with dementia, therefore, and their caregivers have to create meaning. Living with Alzheimer disease involves the creation and re-creation of meaning and identity, and the negotiation of empowerment as part of living with disability (Lyman 1998).

Sabat's (2001) work showed how the social environment can worsen the effects of brain pathology. One aspect of our self exists in relation to other people. It is too easy to position a person with dementia so that he or she is disadvantaged. Sabat calls this "malignant positioning" (Sabat 2006), which plays on Kitwood's (1997) idea of "malignant social psychology." The key is to recognize the possibility that the person with dementia is still capable of making meaning (Sabat and Harré 1994; Widdershoven and Berghmans 2006).

Not everyone agrees that personhood can be maintained in severe dementia (Davis 2004), but that argument seems to reflect too great an emphasis on one aspect of personhood, namely on the notion of relationships. A greater emphasis on the body—as in the situated-*embodied*-agent view (Hughes 2001), as in the notion of the *body-subject,* derived from Merleau-Ponty (Matthews 2006), or the idea of *bodily autonomy* (Dekkers 2004)—might help to correct this fault. So, too, must the person be seen as embedded in a history, irrespective of personal relationships— but partly a bodily history and partly a social history— as well as a psychological, spiritual, cultural, and moral history. The key to person-centered care is that it picks up the multifarious ways in which people with dementia can and must *be-in-the-world* (Hughes et al. 2006). But this approach also depends on others valuing the individual as a psychosocial, spiritual, physical being whose possible participation in practices should not be overlooked (Brooker 2004).

This insight has both philosophical and practical roots, but the important element is that the effects should be practical. The evidence supporting the effectiveness of psychosocial methods to deal with depressed, aggressive, or apathetic behaviors is still only modest (Verkaik et al. 2005), but it is increasing and holds out the possibility of an alternative to a purely pharmacological response (Fossey et al. 2006). The right approach—the ethical one—must be to pursue patterns of practice that do justice to our potential ways of *being in the world* as persons, broadly conceived.

Making Diagnoses

To receive (or to give) a significant diagnosis is an extremely personal thing, which normally occurs in secret, and which brings together scientific and clinicocultural understandings. Continuing the earlier themes, I shall reflect here on the extent to which our clinical judgments are located in the broader context of the world. Clinical practices must square with those patterns of practice that encapsulate our engagement in civil society. Thus, the need to tell the truth, to maintain confidences, to involve significant others, to use our biological explanations to arrive at an understanding of the implications of a diagnosis, and to participate in research primarily for the good of others—all of which stem from making a diagnosis—require practices that cohere with societal and moral norms if they are to be carried out ethically. I shall start by dis-

cussing the new but contentious diagnosis, mild cognitive impairment (MCI) (see also Chapter 9, "Mild Cognitive Impairment").

Mild Cognitive Impairment or Normal Aging?

MCI is problematic from a philosophical point of view (Gaines and Whitehouse 2006; Graham and Ritchie 2006). The main problem lies in the distinction between normal and abnormal aging. There is some evidence that any diagnosis, including the diagnosis of MCI, might be deleterious to the individual; but given that MCI does not inevitably progress to full-blown dementia, the potential harmfulness of the diagnosis is a cause for concern (Corner and Bond 2006). The deeper concern is about the nosological status of MCI. The question can be raised as to whether it is a *real* entity at all. This may, however, miss the point, because—even if socially (or scientifically) constructed—diagnoses remain a reality (Hamilton 2006). The point is that MCI inevitably involves evaluative judgments. There is nothing amiss in this:

> The elimination of culture from the determination of what counts as a disease is not only theoretically impossible, it is not clinically feasible. The clinic is the place at which science and culture meld in concepts, such as disease and health, which are both factual and evaluative. Human interests and values structure medicine—without them there would be no such thing as medicine. What science-based medicine requires is not to be value free but to be free from distortion through the infiltration of inappropriate evaluations. (Bavidge 2006, p. 76)

There is a sense, then, in which the important question is whether MCI works as a diagnosis: does it actually do some good? It certainly has usefulness (Petersen 2006), but it might also induce a type of rigidity into our thinking about the basic biology of aging that could impair our understanding of what is really going on (Kirkwood 2006). There is a real fear that brain aging may be misconstrued because of the labels applied to it (Whitehouse 2006). Indeed, Whitehouse now suggests that the Alzheimer diagnosis should be done away with: it has become a conceptual encumbrance (Whitehouse 2001; Whitehouse and George 2008).

It is, perhaps, useful to recognize that this debate is not, in essence, about MCI, although MCI is its perfect vehicle. The essence of the debate concerns the place of scientific explanations in our lives. How are we to understand aging? As soon as the question is asked, its multilayered interpretation becomes obvious. Aging is a scientific, but also a cultural and social, concept (Kirkwood 1999). The more important issues, to which we shall return, involve how we understand ourselves and the role that science plays in this understanding.

I shall now use the case of Mrs. K to raise a variety of issues pertinent to diagnosis: truth telling, confidentiality, the views of caregivers, and genetic testing and research.

Case 1

Mrs. K is a 72-year-old widow who has been forgetful for a few years, but her memory lapses have started to impinge on her day-to-day activities. She goes to see her doctor, who sends her for some investigations. A diagnosis of Alzheimer disease is made, but her son has previously spoken with her doctor and asked that she should not be given the diagnosis. He feels it will cause her severe depression, because her older sister already has Alzheimer disease and is in a completely dependent state, living in a nursing home. The doctor explains that he can hardly offer Mrs. K appropriate treatment without telling her the diagnosis. The son suggests that her medication could be given to her by a paid caregiver in such a way that she need not know what it is for. The doctor cannot agree, and tells Mrs. K that she has Alzheimer disease, but assures her that all of her medical information will remain confidential. Her daughter then visits the doctor and asks about Mrs. K's treatment. The doctor feels that he cannot reveal confidential information. The daughter persists in asking about her mother's condition, pointing out that since her mother and aunt have Alzheimer disease, it seems to her likely that she will also have it. She wants Mrs. K and her aunt to have genetic testing, saying that she intends to pursue testing too. Mrs. K is unaware of these conversations, but she visits her doctor again to say she would like to volunteer for research into Alzheimer disease in order to be useful to society. On hearing of this intention, both of her children remonstrate, arguing that she cannot possibly be competent to make such a decision.

I shall briefly highlight some of the relevant literature before offering some concluding remarks on the relationship between clinical practices and the world.

Giving a Diagnosis and Telling the Truth

Bamford et al. (2004) found considerable variability of beliefs and practices concerning diagnostic disclosure. Both positive and negative consequences of diagnostic disclosure were reported, but many of the studies contained methodological shortcomings. Another study revealed that most patients referred to a memory clinic were uncertain about the cause of their memory problem, but 86% wanted to know the cause and 69% would want to know if the diagnosis were Alzheimer disease (Elson 2006). A discussion paper stressed that the issue of diagnostic disclosure was sometimes dealt with in a simplistic fashion. As Whitehouse et al. (2004) put it:

> Diagnostic disclosure is a path starting at the patient's baseline awareness level and ending at the maximum amount of tolerable and useful information that the patient can take in and cope with. (p. 125)

The issue of truth telling in dementia was brought into sharp relief by a UK study showing that in 71% of 34 residential, nursing, and inpatient units, medicines were being given covertly to people with dementia (Treloar et al. 2000). Few institutions had formal policies governing such decisions, and 96% of the staff thought the practices were justifiable. In a later discussion paper, the authors expressed their opinion that covert medication could be used in exceptional circumstances (Treloar et al. 2001). They opined that it was important to have a transparent procedure: the patient had to be incompetent regarding the decision, and the decision had to be discussed and properly documented. They contrasted the view that all deception was wrong with the view that the deception might reasonably be used to relieve suffering.

Confidentiality

The issue of confidentiality is not straightforward in dementia. On the one hand, doctors and other health care workers should honor confidential information. On the other hand, dementia affects and involves all sorts of people. From the doctor to the social worker to the care worker in the day center, many people might need to know confidential information (Hughes and Louw 2002a). The complexity of the context suggests that confidentiality should be regarded as a token of trust. With the increase in ways in which information can be exchanged, it seems increasingly important to consider confidentiality. A study conducted by Tracy et al. (2004) found discordant views: professionals valued disclosure to colleagues and family caregivers on the grounds of best interests; patients did not object to information being shared between professionals, but were not happy about disclosure to the family. Families, meanwhile, asked to be kept informed, even without the person's consent. In a world where information might be useful to governments, to insurers, or even to researchers, the need for greater transparency is obvious; otherwise the goodwill that normally accompanies research participation (a gift to society) might evaporate to the detriment of all (Cayton and Denegri 2003).

Caregivers' Views

Although there is considerable research on issues related to family caregivers of people with dementia, often focusing on their own psychopathology, there is relatively little research on ethical issues for caregivers from their own perspectives (Hughes et al. 2002b). When there is some engagement with caregivers, however, it becomes clear that their perspectives are unique and varied (as shown in Table 22–2).

The perceptions of caregivers are unique because of the nature of the relationships they share with the person with dementia (Hughes et al. 2002a). Thus, when a family caregiver feels guilty because the person with dementia has been institutionalized, or because some form of deceit has been used to encourage the person to do something (e.g., go to day care), the guilt cannot be explained away. It is a fundamental breach of the caregiver's usual pattern of practice, which must accordingly be realigned. "Caregiver burden" often amounts to "ethical burden," which often reflects a unique set of perspectives (Baldwin et al. 2004).

Different caregivers may have entirely dissimilar and contradictory views (Baldwin et al. 2005). Frequently, such contradictions reflect differing circumstances. Hence, these might not be diametrically opposed patterns of practice; they might, in fact, reflect similar concerns: to keep the person calm, for instance. One husband goes for walks whenever his wife wishes, as a way to relieve her inclination to "wander." Another husband locks his wife in the house; perhaps this reflects his inclination to keep her at home rather than have her taken to an institution. Understanding his pattern of practice helps us not to condemn him. We might be able to persuade him that there are better ways for him to cope by alerting him to the possibility of different patterns of practice, but at the same time satisfy his deep instincts to keep his wife safe (Hughes and Baldwin 2006).

Genetics

The variety of issues raised by the genetics of dementia has been previously discussed (Post and Whitehouse 1998). Curiously, instead of genetic issues becoming more intense, they seem to have faded. This might be because the genetic influence on the development of dementia has slowly been realized (see Chapter 8, "Alzheimer Disease"). Although a population survey in the United States revealed that 79% of people would be willing to take a genetic test, this proportion fell to 45% for a partially predictive test (Neumann et al. 2001). The actual experience of going for predictive testing is reported to be disappointing, even when counseling can be helpful (Neilson 1999). And, although medical ethicists might argue that people should know their genetic information (Malpas 2005), in the real world there is considerable skepticism about the use of genetics to build up expectations—even when evidence is absent (Hedgecoe 2006). Furthermore, as it becomes more apparent that Alzheimer disease is not a single entity, it becomes less likely that "the gene is the

TABLE 22–2. Areas of ethical concern that emerge for caregivers of people with dementia

Assessment	Avoiding infantilization	Communication
Community resources	Confidentiality	Consent
Constant telephone calls	Constraint	Difficult behavior
Driving	Dual loyalties	End of life
Euthanasia	Feelings of guilt	Finance
Giving up care	Genetic testing	Lack of support
Letting them down	Long-term care	Misunderstanding
Need for information	Professionalism	Providing personal care
Public embarrassment	Recognizing vulnerability	Relationship with doctor
Safe use of medication	Self-care	Sleep deprivation
Taking over tasks	Talking about person as if not there	Taking risks
Telling the diagnosis	Treating the person as a person	Treatment decisions
Truth telling	Use of respite care	Wandering

Source. Derived from Hughes et al. 2002a, 2002b.

essence" (Dekkers and Rikkert 2006). Although the idea of a single genetic cause can function as a heuristic tool, the reality of multicausality and probability ensures that some of the previous worries about genetic information have lessened. Reflecting on the role of genetics in dementia simply alerts us to the broader aspects of causality and luck that operate in the world. Nevertheless, there remain worries that genetic information, if misunderstood, could adversely affect individuals, particularly if the information were to be in the wrong hands. The soundness of such concern is hypothetically clear, but practically uncertain.

Research

The need to pursue research with people who have dementia and the experience of doing so suggest that many are capable of consent "discussions" (Hougham 2005). For many years, it has been recommended that the perspective of people with dementia should be represented in dementia research (Cotrell and Schulz 1993). The problem, however, is consent. A study finding showed that many people with dementia enrolled in a clinical trial, when tested formally, failed a competency test (Pucci et al. 2001). So, however, did their family caregivers who were said to be cognitively normal! This might simply mean that the formal test of competence or capacity is too demanding (Kim et al. 2001). To help legitimize consent, proxy decision makers are sometimes used, but this can be burdensome and difficult for the proxy (Sugarman et al. 2001). People at risk of dementia are supportive of the idea of surrogate decision makers and show discrimination between the risks and burdens of different research scenarios (Kim et al. 2005). Many patients (82.9%) are willing to give up future decision making to their proxies, but often this occurred when the proxy had made a decision about participation in a hypothetical research scenario that was different from the decision made by the patient when faced with the same hypothetical scenario (Stocking et al. 2006).

Advance directives concerning research might be useful, but it also seems important to recognize that a sizable minority of patients do not wish to give up future decision making to their proxies. In any case, with regard to advance directives for nontherapeutic research, there are ethical reasons for doubting that such instruments can compensate for the lack of subject consent when the risks are beyond the minimum (Berghmans 1998). Research ethics committees were sensitive to risk, at least in Sweden, where there was a good deal of agreement despite differences of age, sex, and expertise (Peterson and Wallin 2003). Nevertheless, women and lay people were found to be somewhat more cautious than experts.

A key ingredient in people's consent to research participation is the quality of communication engaged in with the potential participants, people with dementia, or their caregivers (Vass et al. 2003). The ethical issues affecting research participation are, by and large, concerns regarding communication. It may be possible to promote "geriatric assent" by careful attention to communication in order to understand the values and preferences of those involved (Coverdale et al. 2006). If it is to be ethical, we must attend not only to the content of research, but also to the process (Kitwood 1995).

Summary

As noted previously, the real questions must incorporate how we understand ourselves and the role of scientific ex-

planation in that understanding. Science has a lot to say about MCI, but the essential issue involves aging. What is normal? What should we accept? What should we rail against? What is the point of research on aging? It is, surely, to improve the quality of our lives, not simply to increase longevity. But just as there might be limits to the length of our lives, perhaps there are limits to quality. Should we all have warm houses when we are old? Should we be devoid of all wrinkles? These are questions that science cannot answer. Diagnosis is based on scientific principles, but the meaning of a diagnosis, as well as the point of truthfulness and confidentiality, must be understood in a broader domain. The broader context brings into focus the perspective of caregivers. It is the world of human meaning that embeds genetic information. The essence is to be found in the context of the world (Hughes et al. 2006). So, too, the purpose of research involves scientific explanations, but the benefits of research are always to do with human comprehension, in which individual findings have a significance and meaning in the human world. The process of research must be in step with the values of society, but those values gain a purchase if they cohere with our deeper concerns.

The dichotomies here are between scientific explanation, which is typically causal, and human understanding, which has to do with meaning and which is constitutive. It concerns *what* we are as human beings. The patterns of scientific practice must relate to and be coherent with our patterns of human practice. The essential factor is what we are and what we become by what we do.

Making Decisions and Plans

Deciding and planning are important attributes for people negotiating their way in the world. But these qualities come under threat in dementia. Different jurisdictions have diverse ways of dealing with the problems associated with impaired decision making (see Chapter 21, "Legal Issues"). In the following section I will examine decision making in order to make some particular ethical points and then return to a discussion of ethical issues in the context of patterns of practice.

Consent, Capacity, Best Interests, and Advance Care Planning

Valid consent is given (for investigations, treatment, or research) when the person understands what is required, has the capacity or is competent to make the decision, and does so in a manner that is uncoerced. Importantly, but often overlooked, valid consent must also be recurrent: I might consent to live in my nursing home today, but withdraw my consent tomorrow. I should be allowed to do so, even if the practicalities of such a decision need to be negotiated. The key concept in this instance is capacity, which is almost synonymous with competence. There are slight differences between the United States and the United Kingdom (for instance) in the way that these terms are used by lawyers. Leaving such differences aside, however, it is still worth noting the subtle distinction between "capacity" and "competence" as concepts. One of them (capacity in the United Kingdom) carries more legal weight and is tied to the notion of decision making. The other (competence, in the United Kingdom) has more to do with the person's broader abilities. This is an ethical concern. A person may lack a particular decision making ability, but retain the right to negotiate his or her own way in the world. The ethical concern here reflects on our attitudes to other human beings quite generally. "The means by which we evaluate, and arrive at our conclusions about, an ill person's competency may well ultimately be a test of our own competency as thoughtful, judicious, humane human beings" (Sabat 2001). If a person lacks capacity (or is not competent in the required sense), it is up to those providing care to act in that person's best interests. Leaving this framework for decision making, there are three particular ethical points to be made: the first concerns how much information to give; the second involves wisdom, rationality, volitions, and emotions; the third addresses advance care planning, best interests, and personhood (again). All will be related to patterns of practice.

How Much Information to Give

When imparting information to people, a question arises concerning how much information it is right to give. In the United Kingdom, the legal test relies on the so-called Bolam principle: whether a reasonable body of medical men and women would agree. More recently, legal precedent has moved toward basing decisions about how much information to give on the views of reasonable patients. Reasonable patients would probably want to know common side effects and possible life-threatening or major life-altering complications of a treatment or procedure. Whatever the legal test, however, the real issue is more complicated. It must be a clinical decision, reflecting clinical patterns of practice within which many sorts of influences come to bear. And a large part of this practice is ethical.

One can be completely paternalistic and believe that the doctor knows best. Perhaps no doctor would go so far these days, but some might still feel that it is best not to say too much (I was certainly told this in my first few months after qualification!). Alternatively, the ethical coward will

simply print off the full list of side effects and complications and say, in effect, to the patient: "It's up to you!" The virtuous way to deal with "How much?" lies somewhere between these extremes. This concept will, however, seem hopelessly vague to some. The patient should be told as much as the patient needs to know! But how do we determine the patient's needs?

If we leave this question hanging, a similar question arises in connection with coercion. We can be clear that coercion is wrong and, if coerced, the person has not given valid consent. We should not, however, be so inclined to condemn cajoling. The good daughter cajoles her mother into accepting a little more home care. The good son cajoles his father into attending the day center. So, how do we determine when cajoling becomes coercing?

Determining needs and avoiding coercion depend on a type of negotiation and what might be called "moral navigation." These criteria, in turn, depend on effective, careful communication. Determining how much information the patient needs will, in part, be set by objective standards. But it is open to the patient, at any point, to decline further information: "You do what you think is best, doctor." The doctor or health care worker's job is to hear what the patient is communicating, verbally and nonverbally, with careful attention, and then communicate in turn what is required by the individual. This sort of listening and discussing is a negotiation: there is give and take.

Similarly, good sons or daughters negotiate as they cajole their parents into accepting extra help. The extent to which this is a moral navigation should be clear. We might try this way, or that way. We need (with our patients, partners, or parents) to test the ground tentatively—again using good communication—here and there. We try to discern the path that can be trodden. This is a *moral* navigation because we do not force; we are not pushing them against their will; we are trying gently to persuade them genuinely to agree that this way will be safe and best.

Wisdom, Rationality, Volitions, and Emotions

A great trend is to try to produce valid and reliable, operationalized instruments to assess different capacities (Vellinga et al. 2004b). The impulse to do this is strong and is encouraged by the view that capacity and competence are, at root, legal concepts. But they are also human concepts reflecting human abilities and, as such, they are embedded in a rich context of complex meanings—*complex* because human life (even at a personal level) involves history, culture, interrelationships, interdependence, and so on. There is, therefore, always the possibility that the scientifically operationalized or legalistic conception of capacity might be askew as far as human conceptions of incompetence are concerned. Actually, this is precisely what we see. Research shows that there is a difference between global (common or garden variety, but also professional) judgments of competence and the more "precise" estimations made in the course of research (Pucci et al. 2001). The very term "competency" is complex (Marson 2001); judgments are not always consistent (Marson et al. 1997), and they can vary between physicians and family members (Vellinga et al. 2004a). All of which should convince us that, however convenient it would be from a legalistic perspective, these are not value-free concepts.

For instance, decision making, in addition to its cognitive elements, is also volitional and emotional (Charland 1998; Culver and Gert 2004). A good example of this involves the capacity to make a decision about place of residence:

Case 2

Mrs. L is admitted to a hospital having suffered a fall at home, where she lives alone. She is 72 years old and a widow. She is found to have a urinary tract infection and is very clearly confused. Following antibiotic treatment her physical and mental states improve, but she still has cognitive impairment and it becomes clear she has mild to moderate dementia. She wanders on the ward and is disoriented. On assessment in the ward kitchen, she has problems making a cup of coffee. Questions are raised about whether she will be safe at home. When asked, she states emphatically that she wishes to go home, but this leads to questions about her capacity to make such a decision.

It might well be that Mrs. L would fail a purely cognitive test of her capacity to make such a decision. However, the questions that should be asked in order to assess this capacity are by no means straightforward. A key element will be her ability to function. In her own environment, it might become very clear that she can do the things that other people are worried she cannot do (Sabat 2005). In that case, one might say that her volitional capacity is intact. Similarly, even if she cannot recall her address, it might be that she can point to her attachments to the house in which she enjoyed her married life and brought up her family. In contrast, it is possible to imagine Mrs. L passing tests of recall that have to do with her house, but showing a lack of the appropriate volitional abilities. Or, perhaps she demonstrates no emotional attachments to her home when she is taken there, as if she lacks some element of the appropriate emotional force behind what she says. The ethical point is that our insistence on tests of capacity being cognitive simply reflects our *hypercognitive* society, which is intrinsically biased against people with forgetfulness (Post 2000).

At a conceptual level, this discussion should also raise concerns that, despite the fiction that capacity and best interests are separate legal and conceptual entities, nothing is so clear-cut. For instance, in the United Kingdom one of the legal criteria that determine whether a person lacks capacity is if he or she cannot "weigh up" the relevant information as part of the decision-making process. In courts in the United Kingdom, the judgment about a person's capacity is kept distinct from judgments about what might be in the person's best interests. However, the determination of *best interests* means, according to British law, taking into account the person's previous values and beliefs. Clearly, it is difficult to judge how well someone is weighing things up unless one has some understanding of the person's values which, as it were, set the scales in the first place. Thus, judgments about capacity inherently involve judgments about what might be best for the person.

Furthermore, British law states that people are allowed to make unwise decisions. This has been criticized by commentators from the United States on the grounds that some sort of test of rationality ought to come into judgments about capacity (Culver and Gert 2004). Leaving that point to one side—after all, we are allowed to be unwise in ordinary life (consider bungie jumping!)—it is very difficult at times to decide whether someone is simply being unwise or whether they are not weighing things up properly (in which case they lack capacity). Although these points are made in connection with British legislation, they are applicable quite generally. The concepts of capacity and competence are not clearly defined, nor can they be, because they reflect complex phenomena in human lives. The ethical consequence is that judgments based on capacity or competence need to be made with tremendous care, because our humanity depends on it.

Advance Care Planning, Best Interests, and Personhood

Much of what I have stated about capacity and competence transfers to the concept of best interests. *Situated embodied agents* (i.e., persons) are inherently complex and infinitely varied, given that neither two individuals nor their embedding contexts can be identical. The same point was made about quality of life: what is good for a person cannot be circumscribed. There are always additional possible ways in which a person's life might be improved in terms of quality, and there are many and various ways in which a person's best interests might be served.

Immediately, however, a problem of definition arises. Many ethicists seem to define *best interests* in a limited way. According to Holm (2001), a best-interest standard would allow "only those desires to be acted upon that are deemed to be in the best interests of the person with dementia." This is uncontroversial until it is fleshed out:

> We prevent actions based on desires that are detrimental to the best interest of the person in question, and promote actions based on desires that are beneficial. Accepting this as a rule will, however, have the unfortunate side-effect that the range of the person's liberty is restricted to those desires and choices that are either beneficial to him, according to the assessment of others, or inconsequential. Persons with dementia would thus be the only class of people who would not be allowed to make foolish or reckless decisions sometimes, and occasionally act on such decisions. (Holm 2001, p. 156)

But why should it be that best-interest judgments should only rely on "the assessment of others"? Or, more precisely, why should "the assessment of others" not include an assessment of what the person would have wished? Of course, the point might be that, even if the person's own wishes were taken into account, 1) these wishes are then tempered by the assessment of what others think might be best, and 2) it is difficult in the first place to be sure we can know what the other person would have wished for. Both of these points are perfectly valid.

Rather than using them to condemn the use of the best-interest standard, they should be used to emphasize the point that best interests need to be understood broadly. In any case, what could be better than a best interests judgment? Some writers have, for instance, contrasted best interests with *substituted judgments*, which seems to emphasize the point that best interests involve mainly what others think is best, whereas substituted judgments involve others thinking what the person would have thought was best (Dresser 2007). But even a substituted judgment depends on an assessment *by others* as to what the person would have thought was best; and it still remains the case that, just because the evidence in the past was that Mr. F would have done X, we cannot be certain that today Mr. F would not have done Y. Moreover, the change from X to Y might reflect the prior experience of having decided on X in the past (so we cannot use the fact of the X-decision to justify a further X-decision); or the change from X to Y might reflect Mr. F's inclination to accept the judgment of others (even if Mr. F had hitherto been scathing of the advice of others), which goes to show that a rejection of Y-decisions in the past is not a commitment to reject Y-decisions forevermore. People change, often because of their interactions with the world, including the world of others.

If we are going to make decisions for others, we should try to make the best decisions that we can and we should make them in the interests of the person concerned, where these interests are *broadly conceived*. There seems

to be little alternative. What we should guard against is any definition that attempts to stipulate or pin down what will constitute a person's best interests. In British legislation, for instance, *best interests* has not been defined but, instead, a checklist has been proposed to help decision makers *decide* on what might be in the person's best interests. (Table 22–3 shows the checklist, which, although not legally relevant outside England and Wales, nevertheless provides a useful focus on the breadth of the concept of best interests.)

The checklist certainly emphasizes substituted judgments, that is, thinking what the person him- or herself would have wanted in these circumstances. But the checklist also brings in the views of others, albeit primarily only inasmuch as they shed light on the views of the person concerned. Nevertheless, there is more allowed here than a simple estimation of the person's views and, presumably, this is precisely because it is not possible or likely that only one perspective could capture with any certainty the views of the person concerned.

The checklist also allows some seemingly quite objective statements. For instance, the decision may not be motivated by a desire to bring about the person's death. This reflects a political decision not to allow euthanasia or physician-assisted suicide. It does not preclude the possibility of declining life-sustaining treatments. The point is that aiming to end a person's life in an active way is not seen as compatible with the person's best interests. The person's interests might be served by avoiding ineffective and burdensome treatments (even if this ends in his or her dying); and their interests might be served by giving them treatments (for instance, to relieve pain) that also, in accordance with the doctrine of double effect (Uniacke 2007), shorten their lives. But, according to this way of thinking, active euthanasia would simply *end the person's interests* rather than maximizing or enhancing them.

The best-interests checklist in Table 22–2 also acknowledges the then-and-now problem that we came across in discussing quality of life. Is it what the person would have thought was best in the past, or is it what he or she thinks is best now that should count? Those who emphasize *precedent autonomy* (Davis 2002) or *critical interests* (Dworkin 1993) are faced by those who place more emphasis on the person's *experiential interests* (Dresser 1995) or current evaluations (Jaworska 1999). The position I am arguing for—that best interests need to be interpreted as widely as the notion of personhood allows (i.e., without limit, other than within the bounds of what might count for a person)—allows room for the person's previous and present interests to be considered pertinent. And the best-interests checklist overtly acknowledges the importance of past and present for the person. This is as it should be, because all of us are an amalgam of past and present.

TABLE 22–3. Checklist for determining best interests

- Avoid discrimination
- Consider all the relevant circumstances
- Put the decision off (if possible) pending a return of capacity
- Encourage and enable the person to participate as fully as possible
- If the decision is about life-sustaining treatment, ensure it is not motivated by a desire to bring about the person's death
- So far as is reasonably ascertainable, consider the person's past wishes and feelings
- So far as is reasonably ascertainable, consider the person's present wishes and feelings
- So far as is reasonably ascertainable, consider the person's values and beliefs
- So far as is reasonably ascertainable, consider other factors the person might consider (e.g., cultural or religious beliefs)
- If practicable and appropriate, consult anyone named by the person
- If practicable and appropriate, consult anyone engaged in caring for the person
- If practicable and appropriate, consult anyone interested in the person's welfare
- If practicable and appropriate, consult an appointed proxy
- If practicable and appropriate, consult anyone appointed by a court to act for the person
- Decide upon the least restrictive measure
- Seek to balance the concerns of all involved

Source. Based on the Code of Practice to the Mental Capacity Act 2005 (see Department of Constitutional Affairs 2007).

For this reason, considerable weight must be given to advance care planning (Hertogh 2006). It allows a bridge to be built between then-and-now selves, especially if it includes the possibility of well-informed proxy decision makers (Gedge 2004). Inasmuch as they show respect for the person's autonomy, advance directives ought to carry considerable weight (Vollmann 2001). We need to note that advance care planning can take various forms. It might involve a very specific advance directive, which usually refuses treatment. Such an advance refusal of treatment needs to be very specific in terms of both the treatment and the circumstances under which it would be

required. In addition, there is a more general advance statement, which should reflect the person's values, beliefs, wishes, and inclinations. This neither prescribes nor proscribes a specific treatment, but it provides decision makers with a background on which to base their decisions. Finally, a proxy might be appointed to make decisions and, again, it is usually open to the donor of such decision-making powers to specify if there are specific decisions that should or should not be made.

All of this seems fine, and much of it seems to suggest that advance care planning can take away the problems of decision making for people who lack the capacity to decide for themselves. This is a dangerous myth. The dangers are that advance refusals of treatment will be followed without reflection, or that the decisions of proxy decision makers will be abided by uncritically. From this point of view, a general advance statement of values is probably more realistic and useful. It does seem important that any decisions made for others should involve a degree of struggle, because—in the difficult circumstances we are envisaging—there can be no certainty concerning what the person would have wanted. Moreover, it should not be presumed that understanding a person's meaning will be easy. The view that advance care planning straightforwardly settles what should be done is problematic:

> It overlooks the interpretive and intersubjective aspects of decision making…advance directives cannot replace interpretation and communication in decision making, but they can structure communication processes about treatment and care decisions. (Widdershoven and Berghmans 2001)

Elsewhere, Widdershoven and Berghmans (2006) again caution us to not view advance care planning as uncomplicated:

> From a hermeneutic perspective, advance directives should not be seen as objective statements about prior wishes, to be executed when the moment has come, but as vehicles for joint meaning-making, before and during the experience of dementia. As tools, such documents can orient behaviour and symbolize shared practices of care. (p. 190)

Back to Patterns of Practice

The symbolism of "shared practices of care" takes us back to patterns of practice. If we are critical of advance directives, it is because they can symbolize the myth of measurement, the idea that best interests can be pinned down, that decision making can become a simple matter of ticking boxes. An audit of decision making might reasonably measure processes, but the content of decision making sits in the midst of complex practices involving interrelationships and dependencies. The myth that the content of such human practices might be measured runs parallel to the myths that quality of life, competence, or best interests can be measured in any definitive manner.

Instead, we need to look at our patterns of practice. *Living wills* or advance directives do not need to be followed slavishly. However, a pattern of practice that ignored such documents would hardly cohere with one that tried to show respect for autonomy. If living wills are ignored, there are at least some ethical questions to ask (Masuda et al. 2003). My suggestion is that the ethical questions might well be framed in terms of other patterns of practices valued by those involved. One very reasonable response might be that respect for autonomy can be taken too far and, in certain cultures (but in principle, everywhere), respect for the family or acknowledgement of the cultural context should also inform patterns of practice (Chan 2004). The tension between the individual and his or her context cannot be ignored in dementia, where the role of the family may be critical. Consequently, we should develop patterns of practice in which the central ethical thrust should be on good quality communication, facilitation, and interpretation.

Instead of operationalized assessments of capacity, perhaps our patterns of practice should show greater confidence in our innate, global judgments about competence (Werner 2006). Perhaps, too, in relation to consent, it might be better to accept a pattern of practice that involves "bumbling through" (Kapp 2006), where those involved can square this practice with patterns of respect, not just for autonomy, but for dignity, individuality, history, personal connectedness, interrelationships, authenticity, and the like. We would certainly wish to limit the practice of constraint (Kirkevold et al. 2004). For the sake of liberty, new technologies need to be critically considered (Hughes and Louw 2002b). But how risks and benefits are weighed up, in connection with the various forms of wandering (Robinson et al. 2007), in connection with driving (Snyder 2005), or in connection with any other form of activity undertaken by people with forgetfulness or frank dementia, will often be a matter of individual interpretation in specific contexts.

As Agich (2003) made plain, autonomy is often "interstitial": it occupies the nooks and crannies of everyday practice. So, too, with our freedoms and dependencies—we need to examine them case by case and in a high degree of detail. Our patterns of practice comprise accretions of attitude, endeavor, and understanding, which are shaped by public scrutiny in a world of practices. Therefore, for instance, if we wish to pursue dignity for our patients, we need to see how our patterns of practice incorporate,

detract from, or enhance the complex webs of interaction and locution that preserve dignity (Coventry 2006; Pleschberger 2007). In part, this involves seeing clearly the pattern of practice that surrounds our use of the term *dignity,* but this will quickly reveal both an inner and an outer aspect that is in keeping with our standing as agents situated in a public and private field of thought and actions.

Conclusion

The importance of palliative care in dementia is well recognized (see Chapter 19 in this volume). The ethical decision concerns how people with dementia should die. Free of pain, for sure, free of burdensome or ineffectual interventions too—but people should also die with dignity, and there are those who argue that on occasions death can be dignified only if the person can choose when and how to die. Many of the arguments for and against active dying can be found in the debate reported by Keown (1995). But a question can also be raised in terms of our patterns of practice. If a doctor were deliberately to aim at the death of his or her patient, how would that square with other patterns of practice? One immediate answer is to say (whether we are talking about active voluntary euthanasia or physician-assisted suicide) that killing a patient might amount to an act of heroic compassion. This could well be the case. But then we need to ask what the basis of compassion might be: what is the pattern of practice that surrounds our acts of compassion? When a wife visits her severely demented husband in his long-term institution every day, what does this pattern of practice show? How could it be squared with a pattern of practice that allowed people with dementia in long-term institutions to be actively killed? Is there not some basis to our caring or compassion, which turns out to be a pattern of practice that values human life itself and which, therefore, is incompatible with euthanasia or physician-assisted suicide? If so, then to allow active killing of people with dementia would be to disrupt the cornerstone of our civilized and social practices (Keown 2002).

In this chapter I have introduced the notion of patterns of practice as a useful way to discuss ethical issues in connection with dementia. After all, our patterns of practice simply reflect our engagement with the world. How we engage with people with dementia is one manifestation of how we negotiate and navigate our way through the world. We have to interrelate and interact because of our interconnections and interdependencies. Moral navigation requires that the process and content of our negotiations cohere with our deepest human instincts and aspirations, which pattern our lives willy-nilly. Our situated nature as embodied agents in the world points in the direction of unfolding possibilities for people with dementia, but only if the patterns of practice that surround us all are creative and life-enhancing.

KEY POINTS

- Many ordinary clinical decisions are also ethical decisions, just as facts are often value-laden.
- In the real world, what is right or wrong is often determined in the context of our relationships, our dependencies, and our communications, which stand against the notions of autonomy, duties, and consequences often emphasized by standard approaches in medical ethics.
- In addition, virtue theory emphasizes what we become by what we do, which is one of many ways to argue against an incipient ageism that readily infects much thinking about clinical ethics.
- The notion of patterns of practice provides a framework for understanding and justifying moral decision making in the real world, where we look for coherence between the multifaceted ways in which our lives are patterned.
- Patterns of practice provide us with a means of moral navigation, which often depends on careful negotiation, in a world of complex and sometimes conflicting values.

- Underlying our patterns of practice are concepts of personhood, which must be broad in order to counteract the reductionist tendency to think that the quality of human lives, or our capacities and competencies, can be finally pinned down, quantified, or circumscribed.
- Instead, selfhood in dementia should be understood broadly (not purely in relation to cognitive function) as situated in numerous ways (by history, family, culture, and so on), as embodied, agentive, relational, emotional, and spiritual.

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This provides a careful and sustained critique of many of our ways of thinking about ethical issues in old age.

Ashcroft RE, Dawson A, Draper H, McMillan JR (eds): Principles of Health Care Ethics, 2nd Edition. Chichester, West Sussex, Wiley, 2007

A seminal work in the field of ethics and dementia, covering various issues, from the need for hospice care to personhood, as well as some discussion of the nature of our hypercognitive society.

Purtilo RB, ten Have HAMJ (eds): Ethical Foundations of Palliative Care for Alzheimer Disease. Baltimore, MD, Johns Hopkins University Press, 2004

A very important basic treatment of issues surrounding palliative care in dementia, which, in many ways, sums up the key issues regarding good quality dementia care.

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PART VI

Dementias: The Future

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CHAPTER 23

Biomarkers for the Dementias

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Alzheimer disease (AD) is one of the most common disorders of later life. The neuropathological changes shared by AD and other neurodegenerative disorders are linked to the pathological aggregation of misfolded proteins that accumulate as insoluble oligomers, protofibrils, and amyloid fibrils (Forman et al. 2004; Selkoe 2004; Skovronsky et al. 2006). Considerable progress has been made in understanding these pathological processes in neurodegenerative diseases that culminate in dementia. Due to the complexity and overlap of histopathological abnormalities in neurodegenerative disorders (Forman et al. 2004, 2005), valid and robust biomarkers for the early and differential diagnosis are difficult to establish. Most likely, different biological markers and combinations thereof will have specific applications (e.g., early and differential diagnosis, and monitoring of disease progression and of therapy effects). Because therapy is likely to have the greatest impact when dementia is still incipient, and in light of upcoming novel disease-modifying therapeutic strategies, there is an urgent need to identify biomarkers that allow a high diagnostic accuracy and enhanced prognostic prediction (e. g., from mild cognitive impairment to AD), and provide insight into pathways that may be influenced by drug treatment. Because biomarker research is most advanced for AD, many current concepts about ideal biomarkers for neurodegenerative diseases have been influenced by Alzheimer research (Consensus Report 1998; Frank et al. 2003). A large number of single-center studies, and a smaller but increasing number of controlled multicenter trials, have investigated biomarker candidates for AD.

The most promising candidate biomarkers in Alzheimer research are presented and discussed in this chapter. Results concerning biomarkers for other dementias will also be presented.

Definition and Characteristics of Biomarkers

A biomarker is a disease characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Shaw et al. 2007). The Working Group on Molecular and Biochemical Markers of AD aimed to stipulate the relevance of the single biomarkers, and therefore proposed guidelines to achieve this goal (Consensus Report 1998). Accordingly, the ideal biomarker for AD should detect a fundamental

feature of neuropathology and be validated in neuropathologically confirmed cases. It should demonstrate a sensitivity for detecting AD of at least 85%, and its specificity in differentiating Alzheimer patients from age-matched control subjects and from patients with other forms of dementia should reach at least 75%. In clinically diagnosed populations, a higher level of specificity for biomarkers will probably not be achieved for methodological reasons, considering that even the gold standard, the clinical diagnostic criteria, cannot be absolutely specific. The same applies to controls of the same age, given that some of them might have preclinical AD (Morris and Price 2001). In large groups, this fact will inevitably affect the specificity of the results of even the best biomarker. Ideally, a biomarker should be reliable, reproducible, noninvasive, simple to perform, and inexpensive. Positive predictive value should approach 90%. Recommended steps to establish a biomarker include confirmation by at least two independent studies conducted by qualified investigators, with the results published in peer-reviewed journals (Consensus Report 1998).

Although a large number of Alzheimer biomarker studies have been published, the clinical relevance and feasibility of the investigated biomarkers are not completely elucidated (Hampel et al. 2008). Numerous steps are required before a biomarker becomes an asset to clinicians. First, the technical feasibility of the new marker has to be established, including the availability of a validated assay with high precision and reliability of measurement and well-described reagents and standards. Many potential markers have successfully passed this first step. Second, the possible marker has to be evaluated in a relatively pure sample of diseased and comparison groups. This is similar to the phase 2 trial in therapeutics, but the goal here is to make an initial assessment of its sensitivity and specificity. Only a few potential markers have passed this step. In the next step, the new marker must be studied in a more representative population-based sample, providing an assessment of its true diagnostic properties, and thus demonstrating its clinical usefulness. At present, there are several multicenter initiatives with the scope to evaluate new biomarkers in a population-based design.

Methods Used to Identify Biomarkers

Two different approaches exist for the identification of cerebrospinal fluid (CSF) biomarkers: the *candidate* biomarker approach and the *proteomic* approach. The candidate biomarker approach tries to identify a protein or molecule reflecting the neurochemical changes underlying the central pathogenic processes of the neurodegenerative disease. In Alzheimer biomarker research, the candidate approach should reflect the neuronal and synaptic degeneration, the metabolism of amyloid precursor protein (APP), aggregation of amyloid beta (Aβ) with subsequent deposition in plaques, and the hyperphosphorylation of tau, with subsequent formation of tangles. The proteomic approach uses proteomic methods that try to identify biomarkers that can differentiate affected patients from healthy controls and other brain disorders, regardless of whether the biomarkers are directly linked to the pathogenetic processes of the disease. Proteomic methods include 2D electrophoresis, protein chips, or liquid chromatography, combined with mass spectrometry (Blennow 2005).

Using the candidate biomarker approach, the most advanced three CSF biomarkers, total tau protein (T-tau), $A\beta_{42}$, and various phosphorylated tau protein (P-tau) epitopes have been examined in numerous studies, and have been found to have a high diagnostic potential.

Potential Application for Biomarkers

Early and differential diagnosis of dementia disorders, monitoring of disease progression, and response to therapy are the focus of biomarker research. The value of a marker will vary across these purposes. For example, a biomarker may be well suited as an aid to clinical diagnosis, but have little value in monitoring changes over time in dementia. Biomarkers may also contribute to selecting the correct drug treatment. For example, CSF biomarkers allow differentiation between Alzheimer patients with low levels of CSF $A\beta_{42}$ from those with normal levels, and thus could potentially enable physicians to set up the most efficient drug treatment, in this case, affecting APP/Aβ metabolism. Another important use of CSF biomarkers is as a tool for identifying and monitoring treatment effects. The biochemical effect of drugs that slow down the degenerative process without any direct effect on symptoms could be identified on a much smaller patient sample during a relatively shorter treatment period, using biomarkers instead of the usually applied rating scales (Blennow 2005).

The usefulness of a biomarker depends on the purpose for which it is used. Hence, the criteria for usefulness will vary in the function of the application; not each biomarker will be equally suitable for a particular application. Other potential applications are screening for epidemiological

studies and predictive testing. However, the latter two applications will, hopefully, evolve with upcoming preventive therapeutic strategies.

Today, biomarker research is most advanced in the field of diagnosis. The most promising candidates originate from CSF. Therefore, this chapter will emphasize diagnostic CSF markers. Other applications and markers will be mentioned, but results on those must still be regarded as preliminary. Diagnostic biomarkers should improve early and differential diagnosis, particularly when symptoms are absent, vague, or unspecific. Biomarkers should be used in combination with clinical examinations and investigations such as blood tests, computed tomography (CT)/magnetic resonance imaging (MRI), and neuropsychological testing.

Diagnosis of Alzheimer Disease

The most promising candidate biomarkers are Aβ peptides, tau proteins, isoprostanes, sulphatides, and homocysteine. But there are other potential AD biomarkers (Frank et al. 2003) such as APP, apolipoprotein E (APOE), 8-hydroxy-2′-deoxyguanosine, α1-antichymotrypsin (ACT), interleukin-6 (IL-6), IL-6-receptor-complex proteins, C-reactive protein, and C1q protein (see Table 23–1) (Blennow and Hampel 2003; Blennow et al. 2006)

$A\beta_{40}$ and $A\beta_{42}$

Aβ in Cerebrospinal Fluid

Given that all currently known genetic causes of familial AD are linked to increased deposition of Aβ, it seems very likely that Aβ could be a useful marker for the disease (Consensus Report 1998). The soluble Aβ peptide is a component of normal cell metabolism that, if abnormally proteolyzed, becomes insoluble and aggregates in the brain (Mehta et al. 1991). (See also Chapter 24, "The Molecular and Genetic Basis of Alzheimer Disease.") Unfortunately, total Aβ level shows no clear diagnostic utility (Motter et al. 1995). The 42-amino acid Aβ deposits more rapidly than 40-amino acid A protein (Iwatsubo et al. 1994; Wisniewski and Wegiel 1995). Thus, CSF $A\beta_{42}$ seems to be the initial form of extracellular aggregation, and studies have focused on this peptide. There have been about 20 studies conducted on approximately 2,000 patients and controls showing a reduction of $A\beta_{42}$ by about 50% in Alzheimer patients compared with control subjects of the same age without dementia; the diagnostic sensitivity and specificity levels range between 80% and 90% (Blennow and Hampel 2003). A non-age-dependent cutoff level between Alzheimer patients and healthy controls was found to be 500 pg/mL (Sjoegren et al. 2001).

The sensitivity was higher for patients with APOE ε4 allele (83.6%) than for patients without an ε4 allele (54.2%) (Tapiola et al. 2000). Decreased $A\beta_{42}$ levels were also found in patients with vascular dementia (Hulstaert et al. 1999). Many studies have found decreased CSF $A\beta_{42}$ in persons with mild cognitive impairment (MCI) as compared with controls (Andreasen et al. 1999b), but one

TABLE 23–1. Promising candidate Alzheimer disease biomarkers

Analyte	Biofluid
Amyloid beta antibodies	Serum, plasma, cerebrospinal fluid (CSF)
α-Antichymotrypsin	Blood, CSF
Amyloid precursor protein (APP)	CSF
APP isoform ratio in platelets	Platelets
β-Secretase (BACE)	Platelets
CD59	Serum, plasma, CSF
C-reactive protein	Serum, plasma, CSF
CLq	Serum, plasma, CSF
8-Hydroxy-deoxyguanine	Urine, plasma, CSF
Glutamine synthetase	Serum, CSF
Glial fibrillary acidic protein (GFAP) and antibodies to GFAP	CSF
Interleukin-6-receptor complex	Serum, CSF
Kallikrein	Plasma, CSF
Melanotransferrin	Serum, CSF
Neurofilament proteins	CSF
Nitrotyrosine	CSF
Oxysterols	Plasma, CSF
Sulphatides	CSF
Synaptic markers	CSF
S100β	Blood, CSF

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study found increased levels in patients with MCI. Since disorders not related to Aβ plaques, such as amyotrophic lateral sclerosis and multiple system atrophy, are also associated with reduced $A\beta_{42}$ level (Holmberg et al. 2003; Sjoegren et al. 2002), it is not clear if the decreased level of CSF $A\beta_{42}$ reflects the deposition of $A\beta_{42}$ in plaques, or if other processes, such as decreased Aβ production or increased Aβ clearance or proteolysis, are involved.

In differentiating AD from other types of dementia, the specificity level is only approximately 60% (Hulstaert et al. 1999). An autopsy study demonstrated an inverse correlation between $A\beta_{42}$ levels in the CSF and the number of plaques (Strozyk et al. 2003). It was recently shown that subjects with evidence of amyloid plaque accumulation in the brain, as revealed by positron-emission tomography (PET) studies with Pittsburgh Compound-B (PIB), had the lowest CSF $A\beta_{42}$ concentrations (Fagan et al. 2006). However, future studies need to take account of the considerable diurnal fluctuations in CSF Aβ levels (Bateman et al. 2007).

Data on CSF $A\beta_{40}$ levels are less clear-cut. Several studies showed similar levels in Alzheimer patients and controls (Mecocci et al. 1995; Tamaoka et al. 1997). Only one study (Jensen et al. 1999) showed lower $A\beta_{40}$ levels in patients with AD, with a considerable overlap between patients and controls.

In addition to $A\beta_{42}$ and $A\beta_{40}$ in CSF alone, the ratio of $A\beta_{42}$ to $A\beta_{40}$ has been investigated. The $A\beta_{42}/A\beta_{40}$ ratio is reduced in CSF (or, conversely, $A\beta_{40}/A\beta_{42}$ ratio is increased). The reduction of CSF $A\beta_{42}/A\beta_{40}$ ratio seems to be more marked than the reduction of CSF $A\beta_{42}$ alone (Fukuyama et al. 2000; Lewczuk et al. 2004). Additional studies are needed to determine if the CSF $A\beta_{42}/A\beta_{40}$ ratio has a higher diagnostic potential than CSF $A\beta_{42}$ alone (Lewczuk et al. 2004), especially in cases of MCI and early AD.

Thus, $A\beta_{42}$ comes close to fulfilling the criteria for a useful diagnostic test for AD (Consensus Report 1998), but it is of limited value in differentiating AD from other primary dementias.

Aβ in Plasma

The efforts to discover and develop diagnostic biomarkers for AD in peripheral blood, plasma, or serum has, to date, not led to any candidate markers that are close to the diagnostic accuracy achieved by CSF biomarkers. The best-studied candidate biomarker in plasma is Aβ, but the findings are contradictory. Some groups have reported high concentrations in plasma of either $A\beta_{42}$ or $A\beta_{40}$ in AD, with a broad overlap between patients and controls, whereas most groups find no change (Irizarry 2004). Other studies have also reported high plasma $A\beta_{42}$ (but not $A\beta_{40}$) in elderly people without dementia who later developed either progressive cognitive decline or AD (Mayeux et al. 2003; Pomara et al. 2005). In contrast, van Oijen et al. (2006) recently reported an association between high $A\beta_{40}$, low $A\beta_{42}$, and risk of dementia, a result that is in general agreement with the findings of Graff-Radford et al. (2007), who observed a weak association between low plasma $A\beta_{42}/A\beta_{40}$ ratio and risk of future MCI or AD in a healthy, elderly population. Apart from disease-related factors, the opposing results may be due to the fact that $A\beta_{42}$ is difficult to measure in plasma. Additionally, it is unclear what effect Aβ oligomerization has on Aβ concentrations in plasma measured by immunochemical assays. This possible confounder might vary between different methods, which could explain some of the contradictory results in the literature. It is also still unclear whether the disturbed metabolism of $A\beta_{42}$ in the Alzheimer brain is reflected by changes in the levels of Aβ markers in plasma. In fact, Aβ is produced by many different cells in the body, and there seems to be no correlation between the levels of $A\beta_{42}$ in plasma and CSF (Mehta et al. 2001;Vanderstichele et al. 2000). Similarly, other investigations have shown that plasma $A\beta_{42}$ and $A\beta_{40}$ do not reflect Aβ accumulation in the brains of individuals with AD (Fagan et al. 2006; Freeman et al. 2007).

Tau Proteins

CSF Total Tau

Neurofibrillary tangles, consisting of abnormally hyperphosphorylated tau, are core features of Alzheimer neuropathology. Physiologically, tau is located in the neuronal axons and is a component of the cytoskeleton and intracellular transport systems. Due to alternative splicing of tau mRNA, there are six isoforms ranging in size from 352 to 441 amino acids, with molecular weights ranging from 50 to 65 kDa (Buée et al. 2000), encoded by a single gene consisting of 16 exons on chromosome 17q21. Furthermore, at least 30 phosphorylation sites, either threonine or serine, exist on tau extracted from human brain (Goedert 1993). Due to hyperphosphorylation, tau loses its ability to bind to microtubules and to stimulate their assembly, and develops a tendency to aggregate in the form of neurofibrillary tangles (Iqbal et al. 2000). T-tau and truncated forms of monomeric and phosphorylated tau are released and can be measured in the CSF.

Enzyme-linked immunosorbent assay (ELISA) allows measurement of total and phosphorylated CSF tau protein concentration. T-tau, a general marker of neuronal destruction, has been intensively studied over the past 5–10 years. The most consistent finding is a statistically significant increase in CSF T-tau protein in AD. T-tau is two- to threefold higher in CSF of Alzheimer patients compared

with normal controls (Blennow et al. 2001; Shaw et al. 2007). The CSF level of T-tau seems to reflect the intensity of neuronal damage and degeneration (Hesse et al. 2000b). Tau pathology can also be observed in other neurodegenerative diseases (see Chapter 12, "Frontotemporal Dementia"), but differs from tau pathology in Alzheimer patients at the molecular level (Hasegawa 2006). The mean sensitivity in differentiating Alzheimer patients from controls is 84%; the specificity is 91% (Blennow et al. 2001; Hampel et al. 2001; Vanmechelen et al. 2000). An age-associated increase of T-tau protein has been shown in subjects without dementia, and reference values have been established. For normal subjects, they are: <300 pg/mL (age 21–50 years), <450 pg/mL (age 51–70 years), and <500 pg/mL (age 70–93 years), and should be considered when T-tau is diagnostically employed (Sjoegren et al. 2001).

CSF P-tau. Several ELISA methods have been developed to detect phosphorylation of tau protein at different epitopes, such as threonine 181+231 (P-tau$_{181+231}$), threonine 181 (P-tau$_{181}$), threonine 231+serine235 (P-tau$_{231+235}$), serine 199 (P-tau$_{199}$), threonine 231 (P-tau$_{231}$), and serine 396+404 (P-tau $_{396+404}$). Most of the studies have investigated tau protein hyperphosphorylated at threonine 231 and at threonine 181, and a few results have been obtained for serine 199.

The results of several studies showed a good discriminant power for differentiation of Alzheimer patients from control subjects without dementia. For P-tau$_{231}$, sensitivity varied from 85% to 90%, and specificity ranged from 97% to 80% (Kohnken et al. 2000). It is well established that P-tau$_{231}$ appears early in the pathological development of the disease, even before the formation of paired helical filaments in neurons of the hippocampus (Augustinack et al. 2002; Vincent et al. 1998). Phosphorylation at both threonine 181 and serine 199 occurs later, and these are only found to any appreciable extent in intracellular tangles (Augustinack et al. 2002).

The comparative study of Hampel et al. (2004) investigated the differential diagnostic performances of the three different P-tau assays in the same sample and showed that there is a tendency for P-tau proteins to perform differently in the discrimination of other dementia disorders from AD. P-tau$_{181}$ proved to discriminate better between AD and dementia with Lewy bodies at a sensitivity of 94% and a specificity of 64%, whereas P-tau$_{231}$ maximized group separation between AD and frontotemporal dementia with a sensitivity of 88% and a specificity of 92%. P-tau$_{181}$ and P-tau$_{231}$ performed nearly equally well in discriminating Alzheimer patients from healthy controls, whereas P-tau$_{199}$ showed a lower discrimination power.

In a longitudinal study, P-tau$_{231}$ concentration in the CSF declined over time and varied inversely with Mini-Mental State Examination score at baseline; it showed a more pronounced rate of decline with advanced cognitive impairment. However, these results were not confirmed by T-tau levels (Hampel et al. 2001).

In summary, P-tau proteins come closest to fulfilling the criteria for a useful biological marker of AD, but there is a tendency for P-tau proteins to perform differently in discriminating AD from other primary dementia disorders.

Isoprostanes

Isoprostanes, prostaglandin isomers produced exclusively from free radical–catalyzed peroxidation of arachidonic acid (Morrow and Roberts 1997), are hallmarks of oxidative damage to the central nervous system. The results of several studies have suggested a link between neurodegenerative diseases and oxidative damage (Beal 1995). These biochemically stable end products of lipid peroxidation are released by phospholipases, circulate in plasma, and are excreted in urine (Morrow et al. 1992). Thus, they can be measured in CSF, serum, and urine (Pratico et al. 2000). In several studies, researchers have reported that levels of 8,12-iso-iPF2α-VI, an isomer of the F2-isoprostanes (F2α-iPs), are elevated in urine, plasma, and CSF of Alzheimer patients and correlate with memory impairment, CSF tau levels, and the number of APOE ε4 alleles (Montine et al. 1998; Pratico et al. 2000). Some studies revealed no elevation of F2-isoprostanes concentrations in blood and urine (Montine et al. 2000, 2002). Others suggest that CSF F2-isoprostane levels in Alzheimer patients correlate significantly with global indices of brain degeneration such as decreasing brain weight and degree of cerebral cortical atrophy, but not with APOE genotype or the tissue density of neuritic plaques or neurofibrillary tangles (Montine et al. 1999). Changes in MCI subjects have been reported (de Leon et al. 2007).

Thus, although additional studies are needed to confirm and extend these findings in larger patient cohorts, F2-isoprostanes seem to be a significant marker in AD.

Apolipoprotein E

APOE is a 34 kDa polymorphic protein involved in the transport and redistribution of lipids among various tissues. APOE binds avidly to Aβ, and its immunoreactivity has been shown in amyloid plaque cores and vascular amyloid. APOE is of special interest in AD research because the presence of the APOE ε4 allele is a major risk factor for the development of late-onset AD (Saunders et al. 1993). APOE polymorphism seems to be linked with the levels of amyloid deposits in the brain of elderly subjects without dementia and patients with AD (Schmechel et al. 1993). In-

consistent results have been reported so far on the usefulness of APOE as a biomarker. Some studies found reduced CSF APOE (Lindh et al. 1997; Pirttila et al. 1998), even in Alzheimer patients without the APOE ε4 allele (Hesse et al. 2000a). Other investigations found increased levels of CSF APOE (Lindh et al. 1997), even in Alzheimer patients and APOE ε4 allele carriers (Hesse et al. 2000a). Also, results for APOE in serum are conflicting. Whereas some investigations found reduced serum APOE levels (Siest et al. 2000), others reported similar or enhanced serum APOE concentrations between Alzheimer patients and healthy controls (Slooter et al. 1998; Taddei et al. 1997).

Taken together, levels of APOE in CSF and serum seem not to fulfill the criteria for a useful AD biomarker.

α1-Antichymotrypsin

ACT, one of the serine proteinase inhibitors, plays an important role in inflammation. Increased concentration of ACT has been found in AD brain tissue and is a component of senile plaques (Abraham et al. 1988). One study revealed a positive correlation between ACT levels and severity of dementia (Licastro et al. 2000).

Nevertheless, results of other studies of ACT in CSF and serum are inconclusive. Some studies show no difference in ACT concentration in Alzheimer patients compared with controls (Pirttila et al. 1994). Others find increased levels of ACT in Alzheimer patients (Harigaya et al. 1995; Licastro et al. 1995). At present, investigations in MCI are lacking.

It is possible that serum and CSF levels of ACT are independently upregulated in AD, and that measuring serum ACT concentration could be useful as a screening marker. More independent studies, however, are still needed.

Soluble Interleukin-6-Receptor-Complex (IL-6, IL-6R, gp130)

It has been shown that amyloid within senile plaques is associated with activated microglia and astrocytes that express inflammatory proteins and neuroregulatory factors such as interleukin-6 (IL-6). IL-6 has been consistently detected in the frontal, parietal, and occipital cortex and hippocampus of Alzheimer patients, but not of elderly subjects without dementia. IL-6 has been found in diffuse early plaques without neuritic pathology in isocortical (frontal, temporal, and parietal cortex) and hippocampal brain samples of AD brain. IL-6 immunoreactivity is rare in classical plaques and absent in compact or burned-out plaques. Therefore, it has been suggested that IL-6 expression may appear before neuritic changes, rather than following neuritic degeneration (Akiyama et al. 2000).

IL-6 exerts its biological actions by complex interactions with specific soluble or membrane-bound receptors, forming the biologically active IL-6 receptor complex (IL-6RC). The component proteins, in addition to the 19.5 kDa cytokine IL-6, are two membrane glycoproteins, an 80 kDa protein referred to as the ligand-binding α-subunit (gp80, IL-6R, or CD126) and a 130 kDa protein referred to as the nonligand-binding, affinity-converting, and signal-transducing β-receptor (gp130 or CD130). All members of the IL-6 cytokine family (IL-6, IL-11, oncostatin M), leukemia inhibitory factor, ciliary neurotrophic factor, and cardiotrophin-1 share gp130 as a component critical for signal transduction. In the nervous system, IL-6 can be secreted by microglia, astroglia, neurons, and endothelial cells; the IL-6R by neurons; and gp130 by all cells. Gp130 neuropil immunoreactivity was observed in telencephalic structures including the hippocampus, cerebral cortex, and caudate-putamen. Activation of membrane-bound gp130 by IL-6 and the soluble IL-6R were reported to generate a neuronal differentiation signal. Soluble forms of the two receptors ($_s$IL-6R, $_s$gp130) arise by limited proteolysis (shedding) or differential splicing ($_s$IL-6R of 38 kDa and $_s$gp130 of 68 kDa). It has been reported that this soluble complex ($_s$IL-6RC) forms a hexameric structure in solution, consisting of the three different proteins with a 2:2:2 stoichiometry (Frank et al. 2003).

There is a complex regulatory interaction between all $_s$IL-6R components. SIL-6R enhances IL-6 effects by making the ligand accessible to the membrane-bound, signal-transducing β-subunit; however, it has also been shown to augment the action of $_s$gp130, which neutralizes IL-6 signals. There are commercially available bioassays (ELISA) to detect the IL-6RC in biological fluids. Using such an assay, significantly decreased CSF concentrations of sIL-6R (Hampel et al. 2003a) and sgp130 (Han et al. 2002), in the presence of unchanged IL-6 concentrations (Hampel et al. 1998), were found in Alzheimer patients. In addition, these data indicate that the application of multivariate discriminant analysis using combined CSF T-tau protein and $_s$IL-6RC components may add more certainty to the diagnosis of AD (Han et al. 2002). The reported method, however, must be extended to an independent group of Alzheimer patients, subjects with other neurodegenerative conditions, and control subjects to assess its true diagnostic applicability. Interpretation of the relationship between CSF and brain levels of the IL-6RC presently remain speculative, and studies based on simultaneous measurement of corresponding CSF and brain samples are necessary.

C-Reactive Protein

C-reactive protein (CRP) is an acute-phase reactant synthesized in the liver and not normally found in the brain. Some investigators have found CRP in the senile plaques and neurofibrillary tangles of AD patients' brains (Duong et al. 1997; Iwamoto et al. 1994). CRP is upregulated in the brain of AD patients (McGeer et al. 1989). It was reported that control subjects in the upper three quartiles for serum high-sensitivity CRP presented 20–25 years later a threefold increased risk for all dementias combined, AD, and vascular dementia (Schmidt et al. 2002). In contrast, another study showed no difference between persons with AD and those without (Licastro et al. 2001).

CRP might play a causal role, or merely be a marker of inflammatory processes. Whether the association proves to be direct or indirect, CRP measurements may turn out to be an important adjunct for global risk assessment of dementia (Schmidt et al. 2002).

C1q

There is evidence that C1q, a subcomponent of the first component of the classical complement pathway, is, in addition to its normal production in the liver, also synthesized in the brain by pyramidal neurons and glial cells (Shen et al. 1997; Terai et al. 1997). β-pleated, fibrillar Aβ, and, more recently, tau-containing neurofibrillary tangles have been found to directly and fully activate the classical component pathway in vitro in an antibody-independent fashion (Eikelenboom and Stam 1982; Rogers et al. 1992). C1q is one of the most potent of the many different inflammatory mediators that enhance Aβ aggregation (Webster and Rogers 1996). Several studies revealed increased C1q concentration in Alzheimer patients' brains compared with controls (Akiyama et al. 2000), and decreased levels in CSF correlating with cognitive deficits (Smyth et al. 1994).

These results support the hypothesis that complement plays a role in the pathogenesis of AD by potentially triggering local inflammation.

Homocysteine

Homocysteine is a sulfur-containing amino acid and a precursor of methionine and cysteine. For the conversion of homocysteine to methionine, folate and vitamin B_{12} are needed, and for the conversion of homocysteine to cysteine, vitamin B6 is essential (LeBoeuf 2003). Deficiencies of folate, vitamin B_{12}, and vitamin B_6 result in increased levels of homocysteine. Increased levels of homocysteine in serum, in combination with decreased vitamin B_{12} or folic acid, are considered potential risk factors for the development of cognitive impairment (Teunissen et al. 2002). Several studies have shown an association between hyperhomocysteinemia and risk for AD. In the Framingham Study, Seshadri et al. (2002) found that plasma homocysteine levels greater than 14 umol per liter almost doubled the risk of developing AD over an average follow-up of 2.7 years. In contrast, no relation between increased homocysteine concentrations and cognitive decline was observed in a large study with a mean follow-up duration of 2.7 years (Kalmijn et al. 1999). An MRI study suggested that increased homocysteine is a risk factor for cerebrovascular disease, independent of AD (Miller et al. 2002), raising the question of whether homocysteine is directly linked to mechanisms of AD or indirectly, via cerebrovascular disease. Because elevated plasma homocysteine levels seem to be a strong, independent risk factor for the development of dementia and AD, additional large-scale studies are currently in progress.

Oxysterols and Cholesterol Metabolism

Cholesterol is synthesized in the brain, and its metabolism is linked with AD (Hartmann 2001). It has been hypothesized that increased removal of cholesterol from the brain occurs during neurodegenerative processes (Teunissen et al. 2002). Cholesteryl ester levels in the brain are directly correlated with Aβ production (Puglielli et al. 2001), and the β-secretase enzyme, which cleaves APP to give rise to Aβ, is found in cholesterol-rich lipid rafts (Hartmann 2001). The relationship between serum cholesterol and lipid levels and the risk of AD is not clear. In one prospective study, high serum cholesterol in midlife appeared to increase the risk of incident AD (Notkola et al. 1998), but another population-based study found no clear relationship between cholesterol levels and AD (Romas et al. 1999).

Several oxysterols can be measured as indices of brain cholesterol metabolism. Lathosterol is a major precursor of cholesterol, and can be measured in CSF. 24*S*-Hydroxycholesterol is an index of brain elimination of cholesterol, whose levels in CSF and plasma reflect brain production. The plasma levels of 24*S*-hydroxycholesterol overlap markedly between patients with AD and controls (Bretillon et al. 2000), although a slight increase in CSF levels was reported in patients with mild compared with more severe AD or with controls (Papassotiropoulos et al. 2002). Taken together, although measures of cholesterol metabolism do not appear to be diagnostically useful in AD, they may serve as indices of treatment effects and mechanisms in clinical trials. The mounting evidence implicating cholesterol pathways in AD has led to preliminary studies of

statins in patients with AD (Fassbender et al. 2002; Simons et al. 2002). Following treatment with a statin, CSF levels of lathosterol and 24*S*-hydroxycholesterol decreased, but CSF levels of Aβ were not found to be altered.

3-Nitrotyrosine

In the presence of reactive oxygen species and nitric oxide, 3-nitrotyrosine (3NT) may be formed in constituent proteins in the brain. The predominant pathway appears to involve nitric oxide in the presence of superoxide ion to form peroxynitrite. Peroxynitrite, in turn, reacts with tyrosine residues in proteins or with free tyrosine to form 3NT (Hensley et al. 1999). 3NT can be found in CSF in specific proteins such as superoxide dismutate (Aoyama et al. 2000), or can be found as free 3NT. With normal aging, 3NT concentrations in CSF increase modestly from about 0.75 nM at age 40 years to about 2 nM at age 80 years (Tohgi et al. 1999).

In the brains of patients with AD, regionally specific increases in 3NT have been found in the neocortex and cerebellum (Hensley et al. 1998). In the CSF of patients with AD, the concentration of 3NT was reported by Tohgi et al. (1999) to be 11.4 nM, or about sixfold higher than age-matched controls. In this study, concentrations of 3NT in CSF were inversely correlated with Mini-Mental State Examination scores, but did not correlate with duration of disease.

Increased concentrations of 3NT in CSF, along with changes in isoprostanes and 8-hydroxy-2-deoxyguanosine, are consistent with the suggestion that oxidative stress plays an important role in the pathogenesis of AD. It is not yet clear whether the increase in reactive oxygen species with oxidative stress is proximal or distal in the pathophysiological cascade leading to cell death. As with a number of proposed biomarkers for AD, more longitudinal studies are necessary to determine if changes in 3NT in CSF increase monotonically with disease progression, or might have a more complex relationship with disease severity. Even in the absence of a linear relationship with disease severity, measurement of 3NT and other markers of oxidative stress may provide an indirect marker of drug efficacy in subacute clinical trials using putative disease-modifying agents.

Diagnosis of Other Dementias

There have been several studies on the potential of CSF $A\beta_{42}$ to differentiate AD from other neurodegenerative disorders. Compared with control subjects with other neurological conditions, a slight decrease of $A\beta_{42}$ has been described in non-Alzheimer dementias (Galasko 1998). Low levels of $A\beta_{42}$ protein have been detected in dementia with Lewy bodies; the range of $A\beta_{42}$ protein concentrations overlaps with $A\beta_{42}$ concentrations found in Alzheimer patients (Andreasen et al. 1999b; Kanemaru et al. 2000; Mollenhauer et al. 2005; Parnetti et al. 2001; Vanmechelen et al. 2000), but part of the overlap may be due to concomitant Alzheimer pathology. There is also marked reduction in CSF $A\beta_{42}$ in disorders without Aβ plaques, such as Creutzfeldt-Jakob disease (CJD) (Otto et al. 2000), frontotemporal dementia, and vascular dementia (Hulstaert et al. 1999; Sjoegren et al. 2000).

An increase of CSF T-tau was found in a proportion of cases with other dementia disorders, including vascular dementia, frontotemporal dementia, and dementia with Lewy bodies. Other studies, however, revealed normal levels in these disorders (for a review, see Blennow and Hampel 2003). The potential of T-tau is limited in its ability to discriminate AD from other relevant dementia disorders. At a sensitivity level of 81%, CSF T-tau reached a specificity level of only 57% in distinguishing AD from other dementias (Hulstaert et al. 1999; Parnetti et al. 2000). Therefore, T-tau seems an unlikely candidate as a marker for the differential diagnosis of AD.

The supposition that T-tau reflects nonspecific processes of axonal damage and neuronal degeneration is further supported by increased CSF T-tau in disorders with extensive and/or rapid neuronal degeneration such as CJD (Otto et al. 2002). A highly significant increase of 580% was documented in CJD compared with AD patients. At a cutoff level of 2,130 pg/mL T-tau yielded a sensitivity of 93% and a specificity of 100% between AD and CJD (Kapaki et al. 2001).

For differentiating between AD and frontotemporal dementia, P-tau_{231} showed a sensitivity of 90.2% and a specificity of 92.3% (Buerger et al. 2002b). Also, in the differentiation from geriatric major depression, P-tau_{231} showed good results and a higher discriminative power than T-tau (Buerger et al. 2003). P-tau_{181} has been proposed as a potential marker for differentiating AD from dementia with Lewy bodies (Mollenhauer et al. 2005) or vascular dementia (Schoenknecht et al. 2003). In differentiating between AD and Lewy body disease, specificity at a given sensitivity level was improved by P-tau_{181} compared to T-tau (Parnetti et al. 2001; Vanmechelen et al. 2000). Interestingly, it was demonstrated that, despite a very marked increase in T-tau in CJD, there was only a slight elevation of P-tau_{181} (Buerger et al. 2006). This suggests that CSF P-tau is not simply a marker for neuronal damage, like CSF T-tau, but might specifically reflect the

phosphorylation state of tau and, thus, possibly, the formation of tangles in AD.

The 14–3–3 protein has been described as a useful CSF marker for the diagnosis of CJD (Hsich et al. 1996; Zerr et al. 1997). The 14–3–3 proteins are a group of highly conserved proteins involved in the regulation of protein phosphorylation and the mitogen-activated protein kinase pathway. The γ isoform is thought to be specific for nervous tissue (Aitken 1995; Aitken et al. 1992; Moussavian et al. 1997). Several studies reported an elevation of 14–3–3 protein in CSF in patients with sporadic CJD. Reported levels of this protein were high in 95% of sporadic CJD patients (Zerr et al. 1998). However, although the increase of the 14–3–3 protein in CSF is used as a diagnostic test in CJD, research determined that sensitivity and specificity of the 14–3–3 protein test varied between the different subtypes of sporadic CJD, distinguished by electrophoretic mobility of proteinase K-resistant protein (PrP^{sc}) and genotype at codon 129 of the prion protein gene (Castellani et al. 2004). Evidence also revealed that the sensitivity of the 14–3–3 test was higher in patients with molecular features of classic sporadic CJD rather than in patients with the nonclassic CJD subgroups (94% vs. 77%). The difference appeared to be related to the PrP^{sc} type (Castellani et al. 2004).

Early Diagnostic and Prognostic Value in Mild Cognitive Impairment

The diagnosis of MCI (reviewed in Chapter 9, "Mild Cognitive Impairment") is generally applied to elderly individuals who experience cognitive decline but do not meet the clinical criteria for dementia. Many studies have shown that subjects with MCI have an increased risk for dementia. It was reported that 10% to 15% of patients diagnosed with MCI were diagnosed as having AD within 1 year (Petersen et al. 1999). In MCI patients whose diagnosis was converted to AD during follow-up, elevated T-tau levels at baseline were found in a relatively high number of individuals (Andreasen et al. 1999b; Arai et al. 1997b). Memory-impaired subjects who later developed AD could be discriminated by high CSF T-tau with 90% sensitivity and 100% specificity from those who did not progress (Arai et al. 1997a). Longitudinally, elevated CSF levels of T-tau in MCI subjects were found and still remained elevated after conversion to clinical AD. Another study showed that 88% of patients with MCI had elevated T-tau concentrations and/or low CSF $A\beta_{42}$ levels at baseline (Andreasen et al. 2001). Thus, elevated CSF T-tau in MCI may have the potential to predict AD, a finding that was supported by Hampel et al. (2003b). CSF T-tau remained elevated for up to 2 years in mild to moderate AD. Initial and follow-up levels of T-tau correlated strongly, suggesting a stable rate of neurodegeneration during this time period. It is possible that CSF T-tau will decrease over time if there is effective treatment resulting in disease modification and neuroprotection in Alzheimer patients (Galasko 2001).

CSF P-tau_{231} shows promise in predicting cognitive decline and conversion to AD from MCI (de Leon et al. 2002; Ewers et al. 2007). High CSF P-tau_{231} concentration significantly correlated with subsequent cognitive decline and conversion to AD. Therefore, high P-tau_{231} may be a predictor variable for progressive cognitive decline in MCI subjects, but, in addition to P-tau_{231}, old age and APOE ε4 carrier status independently predicted cognitive decline (Buerger et al. 2002a).

Biomarker Combinations

It would seem obvious to combine a specific set of different neurochemical markers to achieve more accurate early and differential diagnosis and to compare the validity of the individual methods. In agreement with this view, combined measurements have higher predictive power than either diagnostic approach alone in MCI settings. The combination of different CSF biomarkers has been evaluated in several studies in which investigators used different algorithms/methods, such as discrimination lines, classification trees, quadrants with cut points, and ratios.

The most investigated combination is the CSF T-tau and $A\beta_{42}$ combination, but other combinations such as CSF P-tau_{181} and $A\beta_{42}$ have shown positive results as well. The combination of biomarkers has shown slightly higher sensitivity and specificity than a single biomarker. The combined use of CSF-tau and CSF-$A\beta_{42}$ markers seems to allow differentiation between AD and normal aging or other disorders such as depression (Andreasen et al. 2001; Sunderland et al. 2003). Several studies suggested that concomitant measurement of CSF-tau and CSF-$A\beta_{42}$ increase the diagnostic precision for AD. Fagan et al. (2007) showed that CSF-tau/$A\beta_{42}$ and P-tau_{181}/$A\beta_{42}$ ratio significantly predicted conversion from cognitively normal subjects to subjects with very mild or mild AD; the researchers proposed CSF-tau/$A\beta_{42}$ ratios as promising antecedent biomarkers predicting future dementia in cognitively normal older adults. Other studies with MCI pa-

tients confirm these results (Herukka et al. 2007). Hansson et al. (2006) found a slightly higher specificity when using the combination of T-tau and the $A\beta_{42}$/P-tau_{181} ratio than with the combination of CSF T-tau and $A\beta_{42}$ in the detection of incipient AD in MCI patients.

New Approaches

A particularly promising new approach focuses on CSF β-secretase (BACE-1), one of the key enzymes responsible for the pathological cleavage of the APP (Zhao et al. 2007; for review see Hampel and Shen 2008). A significant increase was found in BACE-1 concentration and activity in the CSF of MCI subjects compared with healthy controls. Patients with the APOE ε4 risk allele were found to have the highest concentrations. BACE-1 may have value in early detection, prediction, and biological activity of AD (Zhong et al. 2007).

Isoprostanes are also being studied as markers of lipid peroxidation. An increase was found in the CSF of MCI subjects compared with controls, and levels also increased over time. With regard to their diagnostic precision, the CSF markers isoprostanes and P-tau performed better than memory tests (de Leon et al. 2006). However, due to the very demanding analysis method involved, isoprostanes should still be regarded as merely a scientific approach.

Confounding Factors of CSF Biomarkers

A number of potential confounding factors must be considered before a CSF biomarker can be introduced into clinical routine. The concentration gradient of proteins varies along the spinal cord, so concentration levels may vary depending on whether CSF is removed from the cervical region or from the lumbosacral region (Consensus Report 1998). There is also the influence of lumbar puncture hemorrhage, the presence of the protein in plasma and passage over the blood-brain barrier, and the degradation or loss of the protein in vitro after the CSF tap. The material of the test tubes has an effect on the concentration level of the biomarker, because tubes made of glass and hard plastic are more absorbent than polypropylene tubes, and, finally, a decrease in CSF $A\beta_{42}$ can occur after repeated freeze/thaw cycles (Andreasen et al. 1999a; Blennow 2005; Schoonenboom et al. 2005; Vanderstichele et al. 2000).

In order to limit the effects of confounding factors, the Clinical Neurochemistry Laboratory at Sahlgren's University Hospital, Göteborg, Sweden, and the Biochemical Working Group of the Alzheimer Memorial Center, Ludwig Maximilian University, Munich, Germany, have recommended a standardized procedure based on their routine clinical diagnostic tests effectuated during several years (K. Bürger, G. Frisoni, O. Uspenskaya, et al., "The Pilot European ADM Multi-Centre CSF and Plasma Study," 2008).

Several studies suggest the necessity for age-adjusted reference values for CSF biomarkers. Sjoegren et al. (2001) showed that CSF T-tau varied with age. They found higher CSF T-tau with aging, but they did not find age-dependent changes for CSF $A\beta_{42}$. Age-related levels were also found for CSF P-tau_{181} and P-tau_{231}, but not for P-tau_{199} (Hampel and Blennow 2004). Unfortunately, the sample was small, and more studies are required to establish reference values for clinical use.

Perspective on Biomarker Research

Biomarker research is most advanced in the area of AD. The CSF biomarkers T-tau, P-tau, and $A\beta_{42}$ perform well in identifying AD, and have a particularly high negative predictive value (Mitchell and Brindle 2003). For P-tau, this means that a negative test result rules out AD with a probability of almost 90%. Thus, it seems very likely that in the near future CSF biomarkers may become an integral part of routine diagnostic evaluation along with history, clinical examination, and brain-imaging techniques.

Although combined abnormalities in Aβ species and tau may be characteristic of AD, several other mechanisms are thought to contribute to disease progression; for example, the overlapping processes of free radical–mediated injury to diseased regions of the brain (Markesbery 1999), mitochondrial dysfunction, innate immune activation, excitotoxicity, and others (Hardy and Selkoe 2002). Several of these mechanisms have already been approached as therapeutic targets. Although not specific to AD, many groups have proposed biomarkers that reflect these different facets of Alzheimer pathogenesis as a means to quantify disease progression and response to therapeutics.

Because the neuropathological changes in AD overlap with normal aging and with other dementias, it seems improbable that a single specific biomarker will be found for AD or any other neurodegenerative disease. Consequently, the use of a combination of several CSF bio-

markers will increase specificity, if each marker reflects a pathogenic process (Blennow 2005). The development of methods for simultaneous quantification of several biomarkers will gain relevance to improve diagnostic accuracy. First results in this direction are the development of the Luminex xMAP technology (Luminex Corp.) that allows the quantification of T-tau, P-tau, and $A\beta_{42}$ in CSF (Olsson et al. 2005), and the Meso Scale Discovery technology for CSF T-tau, P-tau, and Aβ quantification (Best et al. 2005). These developments indicate that multiparameter testing is the technique of the future. The diagnostic performance of new candidates such as Aβ-derived diffusible ligands and truncated Aβ isoforms could be investigated by these new techniques (Blennow 2005).

Improvement of techniques is also expected in the domain of proteomics. The surface-enhanced laser desorption ionization-time of flight mass spectrometry (SELDI-TOF MS) technique (Tang et al. 2004) and liquid chromatography Fourier-transform ion cyclotron resonance mass spectrometry (Hagman et al. 2005) are examples of promising new techniques. Nevertheless, additional studies are needed to validate the diagnostic power of new and old candidate biomarkers and new techniques. Furthermore, studies following patients to autopsy, which allow correlation of biomarker results with neuropathological findings, are still rare (Clark et al. 2003). These longitudinal studies would permit researchers to corroborate findings in biomarker study.

In several cases, biomarker studies led to unexpected results that opened up new questions; the answers to these questions will probably enhance our understanding of the pathophysiology of AD and other dementias. Other studies on the markers will probably show that some presumed pathomechanisms of marker regulation and expression are more differentiated and complex than currently supposed.

KEY POINTS

- A biomarker should reflect some aspect of the pathophysiology of the underlying disease.
- Dementing illnesses are likely to have multiple underlying pathophysiological processes.
- Multiple markers are likely to have the highest sensitivity and specificity.
- The most promising AD markers at present are combinations of CSF T-tau, P-tau, and $A\beta_{42}$.

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CHAPTER 24

The Molecular and Genetic Basis of Alzheimer Disease

Roger N. Rosenberg, M.D.

Advances in the molecular and genetic aspects of Alzheimer disease (AD) are leading to increasing numbers of potential molecular targets for drug discovery (Rosenberg 2000, 2005). Many of these advances come from studies of familial AD. Although only about 1% of AD cases have an autosomal-dominant mode of transmission, nearly one-half of AD patients have an affected first-degree relative, due to the high prevalence of AD and to the inheritance of one or more risk factors. Early-onset, autosomal-dominant AD results from specific mutations in identified genes, whereas late-onset sporadic AD appears to result from multiple environmental (such as head trauma) and polygenetic influences, including inheritance of the apolipoprotein E (APOE) ε4 allele, which is associated in approximately 50% of cases. The importance of nongenetic factors in AD is underscored by the fact that no more than 60% of identical twins are concordant for late-onset disease (Gatz et al. 2005). Mutations in the amyloid precursor protein (APP) gene on chromosome 21q and of the presenilin 1 (PS1) and presenilin 2 (PS2) genes on chromosomes 14q and 1q, respectively, account for approximately one-half of early-onset forms of autosomal- dominant inherited disease, as shown in Table 24–1.

Mutations of the genes coded by the APP, PS1, and PS2 all affect APP processing, causing a large increase in the self-aggregating 40 and 42 amino acid amyloid beta (Aβ) peptides. These peptides aggregate under the influence of APOE to form amyloid plaques. In all cases, whether early or late onset, familial or sporadic, there is eventual transformation of diffuse amyloid plaques to neuritic plaques,

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TABLE 24–1. Genetic factors in Alzheimer disease

Located on chromosome	Gene abnormality	Effect on function
1 (autosomal dominant) early onset	Missense mutations of presenilin 2 gene	Increased synthesis and secretion of $A\beta_{40}$, $A\beta_{42}$
14 (autosomal dominant) early onset	Missense mutations of presenilin 1 gene	Increased synthesis and secretion of $A\beta_{40}$, $A\beta_{42}$
19 (risk factor) late onset	Inheritance of APOE ε4 allele	Increased Aβ aggregation; destabilizes microtubules
21 (Down syndrome)	Reduplication of APP gene	Overloads APP processing; plaques and tangles by age 40 years
21 (autosomal dominant) early onset	Missense mutations of APP gene	Increased synthesis and release of $A\beta_{40}$ and $A\beta_{42}$

Note. Aβ=amyloid beta; $A\beta_{40}$=40amino acid amyloid beta protein; $A\beta_{42}$=42amino acid amyloid beta protein; APOE=apolipoprotein E; APP=amyloid precursor protein.

Source. Modified from Rosenberg RN: "Advances in the Molecular and Genetic Basis of Alzheimer's Disease," in *The Dementias: Diagnosis, Treatment, and Research*, 3rd Edition. Washington, DC, American Psychiatric Publishing, 2003. Used with permission.

with a core of Aβ surrounded by degenerating neurites and inflammatory cells. Stimulated at least in part by Aβ (Lewis et al. 2001), neurofibrillary tangles of hyperphosphorylated tau protein (P-tau) develop, and there is loss of synapses and neurons in the affected parts of the brain. The direct neuronal toxicity of Aβ in this pathological cascade activates microglial cells (Meda et al. 1995), and induces the proinflammatory cytokines tumor necrosis factor α and interleukin 1β (IL-1β) (Dickson et al. 1993; Griffin et al. 1998), with subsequent formation of membrane-damaging free radicals (Markesbery 1999).

Amyloid Processing

AD may be considered a form of amyloidosis resulting from the abnormal processing of APP, a transmembrane protein whose function is unknown. APP catabolism is a regulated intramembranous proteolytic process involving three enzymes: α-, β-, and γ-secretase. As shown in Figure 24–1, APP is first cut enzymatically by α- or β-secretase. The products of these first cleavages are cut again by γ-secretase, yielding a soluble fragment from the portion of the molecule produced by α–γ-cleavage, and a self-aggregating insoluble fragment ($A\beta_{40}$ and $A\beta_{42}$) from the portion of the molecule produced by β–γ-cleavage. The carboxy-terminal fragment resulting from APP processing translocates into the nucleus and activates gene expression (Cao and Südhof 2001). The activity of γ-secretase depends on a complex of four interacting peptides; these include nicastrin (Yu et al. 2000), aph-1, pen-2, and PS1 for full γ-secretase activity.

Mutations in APP and in PS1 and PS2 increase synthesis of Aβ from APP in the early-onset forms of AD (Tanzi 1999; Tanzi et al. 1996). Aβ peptides are produced by recycling endosomes after internalization of APP molecules from the cell surface (Yamazaki et al. 1995). $A\beta_{40}$ is the most common form of Aβ in human cerebrospinal fluid (CSF) and plasma. $A\beta_{42}$ aggregates into amyloid fibrils more rapidly and completely than does $A\beta_{40}$, and it is contained in both early diffuse plaques and fully formed neuritic plaques (Selkoe 1998). Fibrillar Aβ is neurotoxic in vitro and in vivo (Geula at al. 1998). Deposition of Aβ precedes clinical symptoms of AD and increases over time. The total concentration of Aβ in cortex is elevated early in the course of AD, correlates with cognitive decline, and appears before tangle formation occurs (Näslund et al. 2000). This suggests that abnormal processing of APP to Aβ or abnormal degradation and clearance of Aβ may be the initiating biochemical event. Persons with Down syndrome have an extra copy of the APP gene on chromosome 21 (Masters et al. 1985), leading to overproduction of Aβ and extensive development of plaques and tangles by age 40 years.

Accumulation of amyloidogenic peptides $A\beta_{40}$ and $A\beta_{42}$ is due to increased activity of the proteases β- and γ-secretase in the familial cases that result from APP and PS1 and PS2 gene mutations. Environmental or other nongenetic factors may also affect activities of β-secretase, γ-secretase, and α-secretase, and modify the development of AD pathology. For example, PC12 neural cells in culture-expressing amyloidogenic peptides can be differentiated further with phorbol esters, which increase nonamyloidogenic peptide synthesis (Baskin et al. 1992). Decreased turnover of Aβ peptides may also contribute to late-onset AD. Neprilysin, an Aβ-degrading peptidase, is

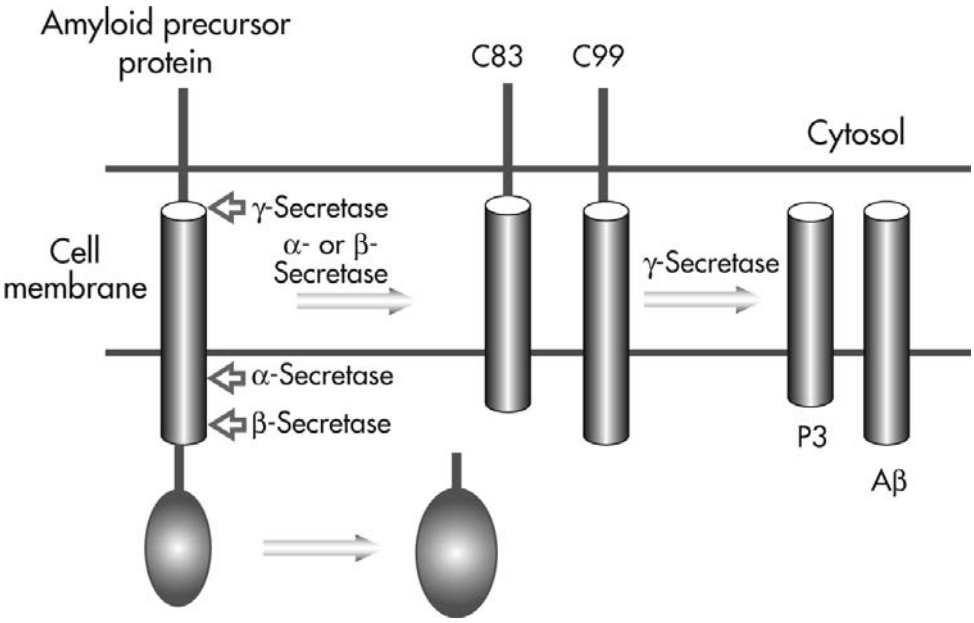

FIGURE 24–1. Amyloid precursor protein (APP) processing.
APP is processed by α- or β-secretase to products C83 or C99, respectively; γ-secretase processes C83 and C99 to P3 and Aβ, respectively. Aβ polymerizes to form oligomers $(A\beta)_n$ in the amyloid plaque. Aβ=amyloid beta.
Source. From Rosenberg RN: "Translational Research on the Way to Effective Therapy for Alzheimer Disease." *Archives of General Psychiatry* 62:1186–1192, 2005. Used with permission of the American Medical Association. All rights reserved.

reportedly reduced in the AD brain in regions enriched for amyloid plaques (Iwata et al. 2001; Yamazaki et al. 1996). Another possible mechanism for increased Aβ synthesis is downregulation of α-secretase, which would reduce production of nonamyloidogenic peptides. The insulin-like degrading enzyme, insulysin, is also important for Aβ degradation and clearance (Farris et al. 2003).

It has not been determined if increased $A\beta_{42}$ synthesis or decreased degradation and clearance contribute to the development of late-onset sporadic AD. Bateman et al. (2006) described a method to determine the production and clearance rates of Aβ in vivo in the human brain. They found the production rate to be 7.6% per hour and the clearance rate to be 8.3% per hour. These are high rates of turnover for a human protein, which suggest that differences found in AD patients might be highly responsive to pharmacological therapy directed at establishing the normal balance between production and clearance of Aβ.

Amyloid Precursor Protein Gene Mutations

Missense mutations in the APP gene located on chromosome 21 cause early-onset, autosomal-dominant AD (Goate et al. 1991; Mullan et al. 1992; St. George-Hyslop et al. 1987). A mutation of codon 693 in this gene causes hereditary cerebral hemorrhage with amyloidosis of the Dutch type (Haan et al. 1991; Levy et al. 1990). APP mutations in codon 717 cause early-onset, autosomal-dominant AD (Goate et al. 1991). A mutation at codon 692 of exon 17 was found in a family with both Aβ plaques and cerebral hemorrhages (Hendriks et al. 1992). At least seven different APP mutations have been found in more than 20 families with early-onset dominantly inherited AD; all missense mutations in the APP gene causing AD are situated at or near α-, β-, or γ-secretase sites and alter regulated APP intramembranous proteolysis.

The Presenilin Genes

Although they are highly conserved throughout evolution, the function of the presenilin proteins is unknown. There is a high homology of the human presenilin genes with sel-12, part of the Notch pathway in *Caenorhabditis elegans* for intercellular signaling during embryogenesis (Levitan et al. 1996). The PS1 gene on chromosome 14 encodes an integral membrane protein of 467 amino acids with 8 transmembrane domains. PS1 was initially found to contain 5 different missense mutations that cosegregated with

early-onset familial AD (Sherrington et al. 1995), and has since been associated with at least 140 different mutations in families with autosomal-dominant AD with onset occurring between age 35 and 65 years. All but two presenilin mutations are missense mutations, and most reside in regions that are conserved between PS1 and PS2 genes. In one series, mutations in the PS1 gene accounted for 66% of autosomal-dominant cases of AD (Raux et al. 2005).

The PS2 gene on chromosome 1 encodes a transmembrane protein of 448 amino acids with 67% overall homology with the PS1 protein amino acid sequence (Sherrington et al. 1995). A missense mutation in this gene has been found in descendants of a single German family that emigrated to Russia and later to the United States (Bird et al. 1988). Two additional missense mutations have been found in an Italian and a Dutch family with early-onset AD (Rogaeva et al. 1995).

Missense mutations in the presenilin genes increase synthesis of Aβ and increase the rate of its own endoproteolysis by 50% (Lee et al. 1997), as shown in transgenic mice and fibroblast cell cultures. The presenilins may direct APP to specific intracellular endosomes containing γ-secretase, preferentially producing $A\beta_{42}$ (Beyreuther and Masters 1997; Cruts and Van Broeckhoven 1998). PS1 mutations increase the activity of caspase (cysteine-dependent aspartate-specific proteases), induce apoptosis, and downregulate the important signaling pathway of the unfolded protein response in the endoplasmic reticulum (Katayama et al. 1999). The increased levels of Aβ in PS1 mutant cells might therefore result from retention of the unfolded APP in the endoplasmic reticulum due to the impaired protein-folding system.

Apolipoprotein E

There are three alleles (ε2, ε3, and ε4) of the gene located on chromosome 19 that encodes the cholesterol transport protein APOE. Inheritance of the ε4 allele of this lipoprotein is a risk factor for late-onset AD. By contrast, APOE ε2 is associated with delayed onset of disease (Corder et al. 1993). APOE ε4 heterozygotes have a threefold increase in risk and homozygotes an eightfold increase in risk for developing AD by age 75 years, compared with APOE ε3 heterozygous individuals (Saunders et al. 1993). However, AD occurs in the presence or absence of APOE ε4. The APOE ε4 allele has been associated with an earlier age at onset in nonpresenilin early-onset AD (Houlden et al. 1998).

The increased risk for AD associated with APOE ε4 may be related to its effect on cholesterol metabolism. In a population-based investigation, Notkola et al. (1998) found that among elderly men, high plasma cholesterol was an independent risk factor for AD (odds ratio = 3.1; 95% confidence interval [CI], 1.2–8.5), after controlling for age and the presence of the APOE ε4 allele. Simons et al. (1998) showed that reducing the cholesterol level of hippocampal neurons in vitro by 70% with lovastatin and methyl-β-cyclodextrin completely inhibited Aβ production while not affecting the generation of APP. The inhibition of Aβ formation was reversed by re-adding cholesterol to previously depleted cells. The requirement of cholesterol for Aβ formation suggests a possible link between cholesterol, Aβ, and AD. Depleting neuronal cholesterol may inhibit Aβ production by removing APP from cholesterol and sphingolipid-rich membrane microdomains, and may reduce the ability of Aβ to self-aggregate (Simons et al. 2001). It is possible that the activity of β- and γ-secretase is affected by cholesterol depletion. Table 24–2 indicates the possible cascade of pathological events in AD.

Transgenic Models

Several human APP genes have been transfected into mouse lines. The human mutant V717F APP gene transfected into a mouse line causes these mice to express high levels of human APP 770, which selectively increases the generation of $A\beta_{42}$ (Games et al. 1995). These transgenic mice develop many of the pathological features of AD, including numerous extracellular Aβ deposits, neuritic plaques, synapse loss, astrocytosis, and microgliosis. The development of Aβ plaques in the V717F transgenic mouse depends on the expression of *APOE*. Knockout mice lacking an APOE gene developed only small amounts of cortical and hippocampal amyloid plaques; there were diffuse plaques that did not display the thioflavine-*S* fluorescence of mature neuritic plaques (Bales et al. 1997). Holtzman et al. (1999, 2000) found that human APOE ε3 and APOE ε4 suppressed Aβ deposition at age 9 months in the APP $V717F^{+/-}$ transgenic mouse, compared with mice lacking *APOE*. By 15 months of age, expression of human APOE ε3 and ε4 in this mouse model expressing APP $V717F^{+/-}$ and mouse $APOE^{-/-}$ resulted in significant fibrillar Aβ deposits. There were at least 10 times more fibrillar deposits in mice expressing human APOE ε4, suggesting that a critical concentration of APOE and Aβ is required for mature fibrillar Aβ to be deposited as plaque.

There also appears to be a relationship between hypercholesterolemia and Aβ deposition in the transgenic mouse, with high levels of cholesterol being related to increased deposition of plaque (Refolo et al. 2000). Al-

TABLE 24–2. Possible pathophysiologic model of Alzheimer disease

The triggering event may be a long-term excess of brain Aβ production over clearance.
This could cause accumulation of toxic oligomers and deposition of Aβ-containing plaques in the preclinical stage of the disease.
Accumulation of Aβ-containing neuritic plaques and hyperphosphorylated tau-containing neurofibrillary tangles are associated with progressive cognitive impairment.
Apolipoprotein E ε4 aids polymerization of Aβ into the beta-pleated sheets of amyloid in plaques.
Single nucleotide polymorphisms in the genes for proteins involved in neuronal cell surface membrane receptor signaling may be linked to Alzheimer disease by misdirecting APP processing and/or Aβ degradation and clearance, and tau hyperphosphorylation.
Late-onset Alzheimer disease results from induction of polymorphic genes associated with environmental factors (e.g., head injury).
Autosomal-dominant Alzheimer disease due to mutations in the APP, PS1, or PS2 genes is associated with increased production of $A\beta_{40}$ and $A\beta_{42}$.
Increased Aβ synthesis in Down syndrome is associated with neuritic plaque and neurofibrillary tangle formation, and is often accompanied by cognitive decline.
Dissolution of amyloid plaque by Aβ vaccination is associated with behavioral improvement in transgenic mice; Aβ vaccination of Alzheimer disease patients slows cognitive loss and reduces brain amyloid burden.

Note. Aβ = amyloid beta; APP = amyloid precursor protein; PS1 = presenilin 1; PS2 = presenilin 2.

though early epidemiologic studies suggested that 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) might help prevent AD by reducing brain cholesterol synthesis, further examination of these studies and the failure of two large clinical trials cast considerable doubt on the usefulness of statins for prevention or treatment (Rockwood 2006).

Monthly immunization for 11 months with injections of $A\beta_{42}$ peptide was found to prevent the development of Aβ plaque formation, neuritic dystrophy, and astrogliosis in mice transfected with the V717F mutant human APP gene (Schenk et al. 1999). Partial regression and clearance of plaques were seen in animals that had already developed them. Substantial reduction of reactive gliosis also occurred. Based on the impressive reduction in brain amyloid burden in the immunized transgenic mice, a safety and efficacy trial of an $A\beta_{42}$ peptide vaccine was initiated in humans. AD patients who were immunized with a primary injection of pre-aggregate $A\beta_{42}$, followed by one booster injection, generated antibodies that recognized Aβ plaques, diffuse Aβ deposits, and Aβ in brain blood vessels. Thus, $A\beta_{42}$ vaccination in AD patients induced antibodies with a high degree of selectivity for the pathogenic target structures (Hock et al. 2002).

Some patients who generated such antibodies showed slower rates of decline of cognitive functions and activities of daily living (Bayer et al. 2005; Hock et al. 2003). The $A\beta_{42}$ immunization appeared to have had a positive therapeutic effect, but the clinical trial had to be terminated because 6% of immunized patients developed an autoimmune meningoencephalitis (Orgogozo et al. 2003). The brains of four people with mild to moderate AD who had been vaccinated and died from unrelated causes were subsequently examined. Each brain showed an almost complete lack of Aβ, with maintenance of neurofibrillary tangles (Beckman 2004; Masliah et al. 2005). The vaccine targeted normal myelin in addition to Aβ, leading to acute demyelinating lesions in some patients (Beckman 2004; Bennett and Holtzman 2005; Orgogozo et al. 2003). The specificity of the Aβ peptide vaccine must be reviewed, given that the role of nonspecific microglial activation by any vaccine reducing the accumulation of Aβ remains an unresolved issue. To prevent secondary encephalitis, a program utilizing passive immunization with preformed $A\beta_{42}$ antibodies is in development.

Gene gun–mediated gene vaccination targeting $A\beta_{42}$ is a method that could potentially be used to prevent and treat AD. Gene vaccination using the cDNA for Aβ in transgenic mice generated antibodies against Aβ without activating the cytotoxic T cells that cause autoimmune meningoencephalitis (Qu et al. 2004). APPswe/PS1ΔE9 transgenic (Tg) mice were immunized with an $A\beta_{42}$ gene construct delivered by the gene gun. The vaccinated mice developed high titers of Th2 antibodies against $A\beta_{42}$ without a significant T cell response. The $A\beta_{42}$ levels in the brain were decreased by 41% and increased in plasma 43% in the vaccinated compared with control mice, as assessed by ELISA analysis. $A\beta_{42}$ plaque deposits in cerebral cortex and hippocampus were reduced by 51% and 52%, respectively, by quantitative immunolabeling comparing treated mice with control mice. Glial cell activation and T-cell infiltration of brain were also significantly attenuated in vaccinated compared with control mice (Qu et al. 2006).

Because immunization therapy for AD has lowered the Aβ burden in selected AD patients, the significant side

effects must be reviewed carefully, and new immune strategies designed, which should include active immunization with the Aβ gene.

Lipoprotein Receptor–Related Protein

The lipoprotein receptor–related protein (LRP) is a member of the low-density lipoprotein receptor gene family. Genetic association studies suggest that reduced LRP expression correlates with increased AD susceptibility and younger age at disease onset (Beffert et al. 1998). The LRP is a receptor that mediates the internalization and degradation of substances involved in the metabolic pathways of lipoproteins. There are eight ligands potentially involved in AD that may interact with the LRP. They include cholesterol, APP, α_2-macroglobulin (Blacker et al. 1998), APOE, the cytosolic adaptor protein FE65, and possibly Mena, Dab1, and Reelin (Cooper and Howell 1999; Hyman et al. 2000). APP-APOE complexes binding to LRP may be an early event in the intracellular routing of APP, and may affect the ratio of nonamyloidogenic APP processing by α-secretase to amyloidogenic APP processing by β- and γ-secretases. The α_2-macroglobulin molecule binds both to Aβ and the LRP (Kristensen et al. 1990; Strickland et al. 1990). FE65 binds both to the LRP and APP. The LRP contains the NPxY motif found in the cytoplasmic tails of many cell surface receptors. NpxY is required for the clustering of the receptor in the coated pits and subsequent receptor endocytosis. Thus, the LRP receptors interacting with cholesterol, APP, Aβ, α_2-macroglobulin, and APOE may be involved in their internalization and subsequent trafficking of molecules to specific subcellular compartments (Trommsdorff et al. 1998). FE65, the peptide promoting APP and LRP binding, in turn binds the protein Mena. An additional protein, Dab1, binds both to APP and to the LRP. As a result, there is a complex of proteins involved in cell transduction that may determine the nature of APP processing and Aβ synthesis.

Tau Protein

The intraneuronal neurofibrillary tangles (NFTs) of AD are composed of hyperphosphorylated microtubule-associated P-tau aggregated into paired helical filaments. Tau normally binds to and stabilizes the microtubular protein that forms the cytoskeleton of axons. When tau is dissociated from its microtubular binding domains, it autopolymerizes, is phosphorylated, and becomes unable to rebind to microtubules. A link has been established between Aβ deposition and NFT formation. Lewis et al. (2001) crossed transgenic mice expressing a mutant P-tau that leads to NFT formation with mice expressing mutant APP and found increased NFT formation in the limbic system and olfactory cortex. By injecting $A\beta_{42}$ into the brains of mutant tau transgenic mice, Götz et al. (2001) were able to increase fivefold the number of NFTs in cell bodies within the amygdala, from which neurons projected into the injection sites. A possible trigger for formation of paired helical filaments is a shift between the neuronal protein kinases and phosphatases that control the phosphorylation state of tau. Protein phosphatase 2A (PP2A), located on microtubules, has been shown to regulate tau phosphorylation *in vivo* (Sontag et al. 1996), and a decrease in PP2A activity has been observed in the brains of individuals with AD (Gong et al. 1995). In addition, alterations in the microtubule binding site of tau due to mutation or posttranslational modification might compromise the ability of PP2A to bind to and thereby serve to dephosphorylate tau (Sontag et al. 1999). Wilhelmsen et al. (1994) found that mutations in the tau gene on chromosome 17 cause a frontotemporal dementia with parkinsonism (FTDP-17), but none of the many tau mutations found in families with autosomal-dominant FTDP-17 have been found in persons with AD.

Hiesberger et al. (1999) studied double-knockout mice lacking low-density lipoprotein (LDL) receptor proteins, very low-density lipoprotein receptor (VLDLR), and APOE-R2. In this strain, there is an increase of hyperphosphorylated tau, linking VLDLR and APOE-R2 expression to phosphorylated tau. Thus, tau hyperphosphorylation may be regulated directly by the APOE-R2–VLDLR signaling pathway, contributing to the disruption of microtubules. A subtle alteration of cellular signals initiated by members of the LDL receptor gene family might affect the stability of the neuronal cytoskeleton and promote neuronal cell death. Hiesberger et al. (1999) also showed that both VLDLR and APOE-R2 can bind reelin on their extracellular domains. Intracellularly, the reelin signal is received by the cytosolic adapter protein Dab1, which contains a protein interaction domain that binds to the cytoplasmic tail of the VLDLR. Reelin stimulates tyrosine phosphorylation of Dab1, and thereby decreases Dab1. The action of reelin on VLDLR and APOE-R2 receptors modulates levels of cytoplasmic Dab1 tyrosine phosphorylation and tau phosphorylation. This has been demonstrated in the mouse mutants lacking reelin, which have increased tau phosphorylation (Hiesberger et al. 1999). It therefore seems likely that tau hyperphosphory-

lation is regulated by the reelin–VLDLR–APOE-R2–Dab1 signaling pathway. When altered, this pathway may induce tau hyperphosphorylation and neurofibrillary tangle formation.

The activity of cyclin-dependent kinase 5 (Cdk5) is also increased in the brain in AD (Patrick et al. 1999). This enzyme is partly responsible for the hyperphosphorylation of tau, reducing the ability of tau to associate with microtubules. Cdk5 activation requires that it associate with its plasma membrane regulatory subunit, p35. A truncated form of p35, p25, also accumulates in neurons in AD brain in direct proportion to the increased Cdk5 kinase activity. This p25-Cdk5 complex hyperphosphorylates tau. The plasma membrane location of p35 also suggests a possible linkage of altered tau phosphorylation with reelin.

Amyloid Biomarkers

Possible biomarkers for AD include elevated plasma levels of $A\beta_{42}$ in individuals over age 65 years (Mayeux et al. 1999). Plasma Aß42 levels decrease as individuals develop AD; CSF levels of Aβ 42 also decrease with disease progression. The decrease in CSF $A\beta_{42}$ levels is associated with a rise in CSF tau, possibly related to increased neurofibrillary turnover and clearance in the CSF. The mean ratio of the 120- to 130-kD APP isoform to the 110-kD APP isoform in blood platelets in patients with AD has been shown to be significantly lower than that of control subjects (Rosenberg at al. 1997) This ratio decreases as the disease progresses (Baskin et al. 2000). In platelets, Tang et al. (2006) showed increased levels of $A\beta_{42}$, increased activation of β-secretase (BACE1), decreased activation of α-secretase, and decreased APP 120 kD/130 kD ratios in AD patients compared with normal control subjects. These observations suggest that the platelet APP is processed by the same amyloidogenic and nonamyloidogenic pathways as in the brain. This alteration in platelet APP processing in AD patients may be a useful biomarker for disease progression and for monitoring responses in clinical trials.

Protective Genes

Just as the APOE ε2 allele appears to delay the onset of AD, there may be other genetically determined factors that protect against AD. Hendrie et al. (1993) reported that AD is rare in the Cree Indian tribe of Canada compared with an urban white population. Henderson et al. (2002) found lower frequency of the APOE ε4 allele in Choctaw Indians. Among Cherokee Indians, as the genetic degree of Cherokee Indian ancestry increased, the representation of AD decreased (Rosenberg et al. 1996). The low prevalence of AD in high-genetic Cherokee Indians was not affected by the APOE ε4 allele. These data suggest that complex protective and disease-causal genetic factors may be involved in a variable manner in AD. Native American tribes are descended from Southeast Asian peoples; thus, it is notable that a lower prevalence rate for AD has been found in the Chinese of Hong Kong than in white populations (Mak et al. 1996). A high incidence of vascular disease may add to the disease burden in some populations (Weiner et al. 2003). Also, Pericak-Vance et al. (1996) reported a low prevalence of AD in another outbred population, the Amish of Indiana, and concluded that this finding is only partially explained by the decreased frequency of the APOE ε4 allele in this population.

Risk Genes

There have been hundreds of reports showing or refuting an association of specific susceptibility genes with AD (Bertram and Tanzi 2004; Bertram et al. 2007; Farrer et al. 1997; Saunders et al. 1993; Tanzi 1999). It is clear that mutations in the APP gene (chromosome 21), PS1 gene (chromosome 14), and PS2 gene (chromosome 1) cause AD. It is also well established that the ε4 allele of APOE is a major susceptibility factor for AD (Farrer et al. 1997; Saunders et al. 1993). However, a clear consensus concerning other susceptibility genes for AD remains to be reached. However, progress has been achieved by Bertram et al. (2007), who have collected systematic analyses of AD genetic association studies in the AlzGene database, a publicly available updated database. They have identified at least 12 potential AD susceptibility genes with statistically significant allelic summary odds ratios (ranging from 1.11–1.38 for risk alleles and 0.92–0.67 for protective alleles).

A major advance in identifying a gene associated with AD was made recently by Rogaeva et al. (2007), who reported that inherited variants in the neuronal sortilin-related sorting receptor (SORL1) are associated with late-onset AD. These variants, which occurred in at least two different clusters of intronic sequences within the SORL1 gene (also known as *LR11* or *SORLA*) may regulate tissue-specific expression of *SORL1*. Rogaeva et al. (2007) pointed out that Aβ generation occurs in several subcellular compartments, and a primary location is during the re-

entry and recycling of APP from the cell surface via the endocytic pathway. Inherited variants in these pathways might influence APP processing and affect risk for AD. These results imply that there are several different AD-associated allelic variants in distinct regions of the SORL1 gene in different populations, and that these variants are likely to be in intronic regulatory sequences that affect the risk for AD by altering the physiological role of *SORL1* in APP processing. *SORL1* appears to play a key role in the differential sorting of APP. With normal *SORL1* expression, APP holoprotein is sustained and recovered via the retromer pathway. However, if *SORL1* is underexpressed, APP is released into late endosomal pathways and processed by β-secretase cleavage, with subsequent γ-secretase cleavage, generating Aβ.

Conclusion

New therapies for AD are critically needed in view of the fact that present therapies are largely supportive. They slow cognitive loss to a marginal degree, but are not directed at the biological basis of the disease. It was reported that immunotherapy using anti-Aβ antibodies with Aβ peptide vaccination had the potential to reduce brain Aβ levels and also slow cognitive loss in Alzheimer patients, but had unacceptable complications. Aβ levels were reduced in several postmortem brains of Aβ peptide vaccinated patients, but there was no clinically meaningful slowing of cognitive loss in patients who developed significant anti-Aβ antibodies (Gilman et al. 2005; Masliah et al. 2005). $A\beta_{42}$ gene vaccination with the gene-gun shows potential, inasmuch as it raises high titers of anti-$A\beta_{42}$ antibodies of the Th2 type without a T-cell immune response, and significantly reduces the level of $A\beta_{42}$ in transgenic mouse brain.

Time matters in most issues, including in the treatment of the AD patient (Rosenberg 2006a, 2006b). It appears crucial to identify presymptomatic AD when soluble Aβ and tau levels predominate and formed plaques and tangles are minimal (Lesne et al. 2006; McLean et al. 1999; Santa Cruz 2005). This may be the only time to reverse the pathology and prevent cognitive loss. Persons now diagnosed with mild cognitive impairment may be the ideal group to treat, given that this condition appears in most cases to be early AD (Morris et al. 2001). High levels of CSF tau and low levels of $A\beta_{42}$ may be useful biomarkers (Andreasen et al. 2001; Galasko et al. 1998). Peskind et al. (2006) provided important data showing that $A\beta_{42}$ —but not $A\beta_{40}$—levels in cerebrospinal fluid are significantly reduced with age in persons who are cognitively normal and positive for the APOE ε4 allele. These findings are highly supportive of the hypothesis that the APOE ε4 allele accelerates pathogenic $A\beta_{42}$ deposition in the brain. Because not all of these persons will develop AD, it will be necessary to correlate these findings regarding CSF with methods to measure Aβ levels in living patients. The task for the immediate future is to sequence the genomes of families with and without AD and seek polymorphisms in a small subset of genes that increase the risk or cause the disease (Tanzi 2000).

KEY POINTS

- Familial dominantly inherited AD is caused in part by the increased processing of amyloid precursor protein to $A\beta_{42}$.
- Late-onset sporadic Alzheimer disease appears to arise from the interactions of multiple environmental factors and genetic polymorphisms.
- Early or prophylactic treatment seems to offer the most hope for arresting or preventing the disease.

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CHAPTER 25

The Future of Dementia Treatment

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As emphasized in earlier chapters, Alzheimer disease (AD) is a devastating condition that affects millions, robbing them of the essence of their humanity. Although treatments do exist, they are limited in effectiveness and further limited by underutilization. There are, in fact, conflicting concepts about the usefulness of these agents, both in AD and in other conditions causing cognitive impairment. However, important research continues to explore the full range of utility of currently approved treatments, including their value in the spectrum of disease severity, possible mechanisms that could underlie extended benefits, and their effects in other dementing illnesses such as Parkinson disease, dementia with Lewy bodies, the frontotemporal dementias, and vascular cognitive impairment.

Developing new treatments will require identifying new targets. Research and, ultimately, treatment may be aimed at interventions for a multiplicity of processes that underlie disease pathology and clinical presentation. And these new targets will be uncovered by our understanding of the interactions among genetic and environmental factors. Processes that play a role in the cognitive and behavioral features of dementia include neuronal death, loss of synapses, axonal changes, and deterioration of compensatory mechanisms such as modification of plasticity and regeneration cascades.

Holding great hope for the future, but truly in its infancy, is the development of treatments that target Alzheimer pathology and aim for a cure. Currently, these approaches focus on synthesis of two proteins, amyloid and tau. Whereas earliest approaches focused on the plaques and tangles themselves, recent exciting work now focuses on the molecular biology and processing of proteins that lead to these accumulated structures. Membrane trafficking, under the control of many proteins, offers an endless number of targets for intervention. Future approaches may include stimulating synaptic connectivity and neural regeneration. Most intriguing is the possibility of coupling these

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approaches with diagnostic techniques to identify precise populations most likely to respond to specific treatments.

Where We Stand With Treatments: Challenge for New Discoveries

Currently approved treatments in the United States consist of the acetylcholinesterase inhibitors (AChEIs) and memantine. AChEIs, first approved in the 1990s, continue to be the mainstay of treatment. Donepezil recently received an extension of its indications to include patients with moderate to severe dementia. This expansion of indication was based on several studies of patients with severe disease. A study of 248 patients in Sweden with Mini-Mental State Examination (MMSE) (Folstein et al. 1975) scores ranging between 1 and 10 demonstrated benefit compared with patients given placebo on the Severe Impairment Battery (SIB) (Schmidt et al. 1997) and on an Activities of Daily Living scale (Winblad et al. 2006). Similar results were reported in a Japanese study and in a multinational study in which donepezil improved both the SIB and a clinical global scale (Black et al. 2007). In trial results reported by Howard et al. (2007) with patients with AD and agitation, no improvement was seen on agitation scores; however, even in this significantly impaired group (with a mean MMSE score of < 10), improvement on both MMSE and SIB scores was noted.

Memantine, approved after the AChEIs, received an indication for moderate to severe disease. Glutamate-mediated toxicity has been implicated in the neurodegeneration of AD. The action of memantine as an *N*-methyl-D-aspartate receptor antagonist may mediate its therapeutic benefit. To date, this indication has not been extended to mild dementia, and a review of all data suggests only minimal support for an expansion (Raina et al. 2008).

The availability of approved treatments for dementia does not adequately capture "where we stand," because, in fact, there are many indications of gross undertreatment. Despite persistent evidence of benefit of treatment, Lucca et al. (2006) report an inverse relationship between percentage of patients treated and their ages. Thus, as the prevalence of disease increases with age, the likelihood of receiving approved treatments decreases. Others have argued that flawed methodology of treatment trials leaves open to question the efficacy of dementia treatments, particularly AChEIs, despite the fact that most reported studies show benefit (Kaduszkiewicz et al. 2005). Most disturbing is the National Institute for Clinical Excellence recommendations for the use of drugs to treat AD in the United Kingdom (National Institute for Health and Clinical Excellence 2006), which indicate that AChEIs should be used only in patients with AD of moderate severity (MMSE scores between 10 and 20), and that memantine not be used at all. Although patient and advocacy groups are protesting these guidelines, there is clear evidence of dissatisfaction with efficacy and a demand for more apparent benefit.

Potential Targets for Treatment

As indicated in Chapter 8, "Alzheimer Disease," the hallmark neuropathology of AD is the presence of amyloid plaques and neurofibrillary tangles; modification of these entities may be reasonable targets for interventions in AD.

Modulating Amyloid

Drug development has largely focused on reduction of amyloid plaque. There is considerable interest in the oligomeric form of the plaques' constituent protein, amyloid beta (Aβ), which is toxic to neurons and contributes to memory loss in animal models (Lesne et al. 2006). Moreover, this form of the peptide has been thought to initiate a cascade of events that contribute to activation of microglia, synaptic degeneration, oxidative injury, and apoptosis, each of which contributes to neuronal damage and may be additional targets for intervention. Interventions that reduce amyloid plaque burden, either by altering amyloid metabolism through enzyme mediation or by maximizing clearance (particularly through immunization), are widely proposed, though not so widely realized.

Enzyme Modulators

Events in the metabolism of amyloid precursor protein (APP) may determine the likelihood of the plaque formation. Cleavage of APP by the enzyme α-secretase leads to the formation of nonamyloidogenic, soluble APP (sAPP). When APP is cleaved by β-secretase, plaque-forming Aβ is created. Another enzyme, γ-secretase, also has a role in amyloid formation. Cleavage by this enzyme results in the formation of a small peptide, $A\beta_{42}$, which is highly likely to aggregate and form plaque. Modulation of these enzymes results in differential rate of amyloid plaque formation. Interventions that reduce the production of toxic Aβ could be realized with β- and γ-secretase inhibitors, or by preferentially enhancing α-secretase activity to produce nontoxic Aβ forms. The tricky task is achieving these manipulations while avoiding mechanism-related toxicity.

Perhaps the most advanced approach to enzyme manipulation in terms of clinical experience is γ-secretase inhibition. Selective enzyme inhibitors are being studied in clinical trials, with reports of Phase II studies and Phase III under development. A Phase II study has been completed on the compound LY450139 (from Eli Lilly), which demonstrated relative tolerability and decreased plasma levels of Aβ (Siemers et al. 2006); a Phase III study began in 2008 (more information is available at Clinicaltrials.gov; search: NCT00594568). Another agent, scyllo-inositol, in Phase II clinical studies sponsored by Elan Pharmaceuticals, may perform through γ-secretase inhibition (more information is available at Clinicaltrials.gov; search: NCT00568776).

Several reports of β-secretase inhibitors in animal models have been described. For example, memapsin 2 has been found to reduce Aβ in mouse models (Chang et al. 2007). Another study of a β-secretase inhibitor described lowering of Aβ levels in transgenic animal models using a low-weight molecule that might reduce toxicity (Patrick et al. 2006). Effects of site-directed antibodies targeting the β-secretase cleavage site of APP in cell culture studies indicate that this mechanism produces 50% reduction in Aβ levels consisting primarily of $A\beta_{42}$ and C-terminal fragments of APP (Arbel and Solomon 2007).

The α-secretase pathway regulates protein phosphorylation and produces the relatively nontoxic sAPP. Stimulation of protein kinase-C through steroid hormones such as 17b-estradiol or dehydroepiandrosterone has been shown to stimulate this pathway. Similar signal transduction systems have been proposed as treatment interventions, despite the fact that clinical trials examining these approaches have not yielded benefits.

AChEIs have been assessed in some of these biological models, and indirect evidence suggests that they may stimulate α-secretase pathways leading to nonamyloidagenic peptides. Support for this connection starts with evidence that cholinesterase itself enhances overexpression of Aβ in the APP23 transgenic mouse (Nitsch et al. 1992). Other data indicated that cholinesterase inhibitors in this transgenic model improve mouse performance in the water maze (a learning task) (van Dam and De Deyn 2006). Several studies have examined cerebrospinal fluid (CSF) of patients receiving cholinesterase inhibitors to determine if there is benefit on markers of the amyloid cascade. An early report on the AChEI tacrine identified a small subset of responders in a year-long study, and reported findings of CSF biomarkers for increased secretion of sAPP (Clark et al 2001). Others who have investigated AChEIs have not seen these changes in short-term trials (Parnetti et al. 2002). This evidence, though weak, supports the notion that long-term use of cholinesterase inhibitors might have disease-modifying effects.

Tau Protein

The neurofibrillary tangle (NFT), composed of phosphorylated tau protein, is also a hallmark pathological finding of AD research, and has been suggested by some to be a better treatment target than amyloid. Several studies suggested that the development of NFTs is the earliest neuropathological change in AD (Haroutunian et al. 2007; Terry 2004) Recent commentaries on the neuropathological diagnostic criteria (Consensus Report of the Working Group 1998; Murayama and Saito 2004) suggest that the density of NFTs, particularly in the entorhinal cortex, be considered when establishing a diagnosis of AD. Some have argued that increasing concentration of conformationally altered tau increases with dementia severity. Other investigators reported that abnormally phosphorylated tau levels rise even before NFT formation, and can be documented in brains of subjects with mild cognitive impairment (MCI) as well as those with AD (Haroutunian et al. 2007). The correlation of this marker with cognition throughout the span of the disease makes it a very exciting target for intervention. Hyperphosphorylated tau is also known to interfere with microtubule assembly, which may promote neuronal network breakdown (Geschwind 2003). Several mechanisms for targeting tau that have been considered include inhibitors of tau kinases, such as GSK-3 (Engel et al. 2006) and CDK-5 (Noble et al. 2003), and agents that directly support microtubule assembly. These manipulations have not been conducted in humans; but drugs with these mechanisms, which have other indications in humans, are being assessed in animal models. An example is paclitaxel (Taxol), an anticancer drug that is cell-cycle specific (see the section "Cell Cycle" for more information) and has been associated with microtubule stabilization in cell models. This agent or ones like it may potentially show a benefit in treating AD and other tauopathies (Butler et al. 2007). Lithium, another agent approved in humans, reduces tau phosphorylation, tau accumulation, and axonal degeneration in animal models. Although epidemiological studies suggest that lithium offers some benefit, this has not been demonstrated in clinical trials (Nakashima et al. 2005). Tau mechanisms are worthy of further exploration as therapeutic targets.

Metals

There is some evidence that there is abnormal iron accumulation in the brain, and that this occurs early in the course of AD, prior to the development of the hallmark neuropathology. This evidence has led to the hypothesis that iron accumulation contributes to the pathogenesis of

AD, and that iron chelation might be a therapeutic mechanism. Experimental evidence from a single-blind trial of 48 subjects with probable AD who were randomly assigned to receive desferrioxamine (DFO), 125 mg intramuscularly, two times a day, 5 days per week, for 24 months, indicated that the mean rate of decline was slower in the treated than in the placebo group (Crapper et al. 1991). However, DFO, a large, hydrophilic molecule, is poorly absorbed across the gastrointestinal tract and blood-brain barrier. Clioquinol, a metal-protein-attenuating compound, slowed cognitive decline in Alzheimer patients and significantly reduced Aβ in transgenic mice; but this agent, originally developed as an antibiotic, is highly toxic (Ritchie et al. 2003). The next generation of these compounds, identified by structure-activity-relationship assays, includes PBT2 (an agent from Prana Biotechnology Ltd.), which was reported as safe in a Phase II clinical trial. Evidence showed use of PBT2 reduced $A\beta_{42}$ in the CSF of patients with AD, and improved patients' scores on executive function tests (Lannfelt et al. 2008). These preliminary results will undoubtedly support larger trials. Chelation therapy with spell ethylene-diaminetetraacetic acid has also induced some improvements in AD patients. An active ingredient in green tea, epigallocatechin gallate, which operates as both an antioxidant and metal-chelating agent, has been associated with better cognitive function and lower prevalence of dementia in epidemiologic studies. In light of this evidence, interest in nontoxic, brain-permeable, iron-chelating drugs has grown (Kuriyama et al. 2006).

In a review, three drugs in particular have been described in preclinical studies: VK28, the prototype iron chelator; M-30; and HLA-20, derived from VK28, which may be effective in iron chelation and radical scavenging (efficacy close to DFO). So far, there are no human data on these compounds, but in vitro and in vivo mouse models have shown neuroprotective and neuron rescue capacity, with M-30 displaying consistent superiority to HLA-20. It is noteworthy that the green tea–derived epigallocatechin gallate (EGCG) has equivalent iron-chelating potency to DFO, M-30, and HLA-20. In vitro experiments demonstrate that M-30, HLA-20, and EGCG induce cell cycle arrest, suggesting that their neuroprotection is at least partially attributable to their capacity to interfere with cell cycle progression. In a transgenic mouse model, forced cell activation has been shown to cause Alzheimer-like pathology, including neurofibrillary tangles, amyloid deposits, and neurodegeneration (Amit et al. 2008). (See the section below for further discussion of cell cycle.)

These data suggest that iron chelators may be considered potential therapeutic agents in AD, targeting early cell cycle anomalies and reestablishing the synaptic connection loss in the injured neuronal cells. Certainly, the data look promising.

Cell Cycle

Another approach to identifying targets for intervention in AD and other neurodegenerative diseases comes from the cell cycle hypothesis. This approach may have downstream effects that could modify both Aβ and tau deposition without direct modulation of enzymatic pathways, thus avoiding adverse effects. This hypothesis is based on the notion that disturbances in mitogenic signaling and cell cycle control could be responsible for neuronal pathology. Several mechanisms that disturb mitogenic signals in cell cycle mediation include excitotoxicity, pro-inflammatory processes, and elevations in growth factor release, all of which have been targeted by agents both in clinical and preclinical work. Both AChEIs and memantine could theoretically act through these mechanisms, since the former is known to arrest mitosis in cell cultures and the action of the latter is predicated on modulation of excitotoxicity through glutamate antagonism. However, the hypothesis may permit identification of other candidates that would more effectively and directly modulate cell cycle activity.

According to the cell cycle model, neurons undergo cell cycle progression in AD to the point that DNA replication occurs. Targets could be selected for their ability to abort the progression through the cell cycle at an early stage, thus avoiding the replication that may be responsible for the processes such as protein metabolism gone awry and inefficient enzyme activity. Ideally, molecular biology would provide a complete map of neuronal cell cycle, identifying precise targets for effective intervention that avoids the degenerative progression. However, the currently identified classes of drugs known to interrupt the cell cycle are also likely to stimulate apoptosis. Thus, a possible agent that could be used to treat AD would have to demonstrate neuroprotection. In acute models of neurodegeneration, protection is demonstrated by agents such as flavopiridol, an experimental drug derived from a medicinal plant from India and retinoic acid, approved for dermatologic indications, (Pepper et al. 2003; Wu et al. 1996). Other agents, such as statins and peroxisome proliferator-activated receptor-gamma agonists also have similar cell cycle interruption properties (Heneka et al. 2005; Murakami et al. 2001). Although the approach of selecting for interruption of cell cycle might be useful, other features would have to be assessed, including brain penetration, suitability for chronic administration, and optimal routes of metabolism. Furthermore, many agents developed as short-term chemotherapies may have adverse effects that would not be tolerated in long-term use. In el-

derly individuals at risk for AD, it is likely that multiple comorbidities and the use of multiple medications will increase the concern about drug-drug interactions.

Our current understanding of processes underlying the neuronal cell cycle is not sufficiently advanced to identify targets for the development of novel therapeutics. However, the use of ligand-centered pharmacological approaches already suggests that identifying existing compounds capable of arresting abnormal entry into the cell cycle may yield new neuroprotective agents, which can be examined in animal models and validated in human trials.

Putting It Together: Personalized Medicine

With the availability of treatments for dementia comes the challenge of using them judiciously. Currently, the only condition for which there are approved treatments is AD. Yet, in the eagerness to treat, there is evidence that the same class of drugs is used to treat a wider array of diseases, including Pick disease, vascular cognitive impairment, and even MCI. The current treatments are in fact targeted to treat by increasing neurotransmitter activation, and this mechanism may have symptomatic benefit in many conditions, including normal aging.

The concept of personalized medicine—for example, forecasting, diagnosing, and treating based on an individual's molecular biological profile—holds great promise for better outcomes. There are at least three potential ways in which biologic markers could be used to direct medical treatment in AD: to diagnose and predict progression with greater accuracy; to select treatments with best sensitivity; and to identify interactions (such as drug-drug, drug-environment, etc.) that could compromise treatment by exposing one to adverse outcome. The potential for such personalized decisions is already available in some conditions, and with additional research they may be available for AD and other disorders.

The future may hold knowledge of genetic profiles that could identify susceptibility to specific diseases. At present, the knowledge base of genetic information is not complete, nor is there an understanding of the gene-environment interaction that might lead to a specific pathology or disease expression. Currently, clinical care in other medical areas uses molecular or genetic markers to tailor treatments to maximize efficacy. For example, use of biological markers can now help physicians optimize breast cancer therapy or better manage dosing of anticoagulants.

Several genetic markers can be used to differentiate dementias or predict progression. Perhaps one of the best established is apolipoprotein E, in which the ε4 allele has a very high association with AD. In several studies of subjects with MCI, in which rigorous neuropsychological testing was employed, the presence of apolipoprotein ε4 allele improved prediction of AD. The identification of neuronal sortilin-related receptor SORL1 gene (also known as *LR11* or *SORLA*) is another marker related to AD (Rogaeva et al. 2007). *SORL1* directs trafficking of APP, and when *SORL1* is underexpressed, APP processing favors Aβ-generation. Identification of such specific receptor abnormalities may provide specific targets for intervention.

The growing technology of neuroimaging offers another aspect of personalizing treatment. The availability of ligands to label Aβ expands the possibility of approaches to treatment and, possibly, prevention. Consider that positron emission tomography (PET) imaging with ligands such as Pittsburg compound B can identify and quantify amyloid accumulation in the brain, even among those without cognitive impairment (Mintun et al. 2006). As confidence grows that brain amyloid is a legitimate target for intervention, one could use this imaging to identify individuals most likely to benefit from such interventions. Furthermore, the imaging might play a role in quantifying the efficacy of treatment with the quantification of reduction in Pittsburg compound B–labeled amyloid as an outcome.

Genetic Markers to Improve Diagnosis

One example of using genetic markers for the diagnosis of AD (see also Chapter 23, "Biomarkers for the Dementias") was reported by Ray et al. (2007), who described a panel of 18 plasma-signaling proteins that could separate AD patients from normal subjects, and those with other dementias. In a second test, the profile of the 18 markers predicted conversion from MCI to AD; the specific proteins were regulators of hematopoiesis, immune responses, apoptosis, and neuronal support. A genetic test that could predict those who will most rapidly progress to dementia would have great utility as a clinical diagnostic tool. As a selection criterion for clinical trials in MCI subjects, it would allow identification of a rapidly converting group, maximizing the ability of the trial to see a drug effect in a brief period of time. Furthermore, if the marker identified a biological mechanism that was etiologically linked to the disease, treatment could be targeted to that mechanism.

Genetic Markers for Treatment Selection

This chapter and several others in this volume have pointed to an array of targets and mechanisms that appear to be relevant to AD pathology and symptoms. These include molecules such as Aβ and tau, and the enzymes involved in misprocessing these molecules to toxic forms. As we identify the genes responsible for these molecular inefficiencies and aberrations, we can imagine individualizing treatment based on genetic profiles. The likelihood of a given mechanism being the best to target within an individual could be determined by such a profile. Targeting isolated proteins may be too simplistic for effective intervention in most patients, but the use of an array of genetic markers to select precise treatment options may be imminent.

Genetic Markers to Maximize Safety

Safety issues are the greatest challenge to both treatment and drug discovery. Adverse drug events are common, and though often attributed to misdosing, at least one-half are likely to be due to genetic causes (Classen et al. 1997). To date, treatments for AD are associated with side effect rates as high as 50%. Although these may be manageable, the absence of a test to identify who might experience such side effects can cause drug and dose selection to require a trial-and-error approach. The situation in drug development is equally challenging. Adverse events were the cause of discontinuing many promising therapeutic approaches, including immunotherapy. If researchers could predict such risks, subjects could be selected for trials with some degree of confidence that safety is being maximized. There are many examples of clinically relevant genetic polymorphisms that predict drug metabolism and direct therapeutic choices in other disease areas, which allows researchers to move away from agents that result in side effects or low efficacy.

The Present and Near Future

In many ways, physicians already practice personalized medicine in the diagnosis and treatment of cognitive disorders. Recognizing that patients respond differently to treatments, doctors routinely use diagnostic tests to learn more about the patient's disease, and choose specific treatment options and drug dosages based on the results of those tests, as well as the patient's family medical history, comorbidities, and lifestyle factors. In the area of AD and other diseases affecting cognition, there has long been interest in identifying profiles that detect and correctly classify those with disease. Neuropsychological testing has long been valued for its ability to improve the distinction between different types of cognitive loss and dementias. The characterization of MCI that predicts advancement to AD has been defined by specific impairment in memory testing using normative definitions, which are the tool of neuropsychology. There is evidence that additional neuropsychological profiles may also predict other dementias (Busse et al. 2006). Though not diagnostic, the use of apolipoprotein E genotyping in addition to clinical history and examination can provide confirmation for diagnosis even at the mildest stages of cognitive impairment (Casseli et al. 2007). As new biomarkers become available, they will create a road map for directing therapy and management plans. Until then, our conviction that such molecular profiles can be identified provides support and motivation for research in these areas.

KEY POINTS

- The currently available treatments for Alzheimer disease are underutilized.
- Treatment of Alzheimer disease may have to be directed at more than one pathophysiological mechanism.
- Therapeutic interventions may target amyloid accumulation via enzyme modulation, immunologic approaches, and anti-aggregation agents.
- Phosphorolated tau and tangle formation may precede symptoms in dementia.

- Newly identified genes associated with late-onset Alzheimer disease may identify proteins to target with experimental agents.
- Profiling with neuropsychological tests, genetics, molecular biology, and neuroimaging may permit an individualized approach to treatment and prevention of cognitive loss and dementia.

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CHAPTER 26

Prevention of Dementia and Cognitive Decline

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Dementia and Public Health: Prevention Is Preferable to Treatment

The implications of dementia as a public health problem can hardly be overemphasized. Alzheimer disease, which causes the large majority of all dementia, affects 2.5–4 million people in the United States and more than 24 million worldwide (Evans et al. 2003; Ferri et al. 2005). Each year Americans spend more than $100 billion on Alzheimer dementia (almost 10% of all health care costs), making it the country's third most costly health condition after cancer and heart disease (Winblad et al. 2005). Among the oldest elderly, the population attributable risk of death with Alzheimer dementia exceeds that with heart disease or stroke (Aevarsson et al. 1998; Tschanz et al. 2004). The public health threat of Alzheimer disease has been recognized for more than 30 years (Katzman 1976) and has led to increasing efforts at prevention. Without prevention, the problem of Alzheimer dementia will only become more extreme as its incidence doubles with each 5 years of age, implying ever-larger numbers of cases as populations age (Jorm and Jolley 1998).

The principal measure of burden for a health condition is *prevalence,* or the proportion of those at risk who are affected. It is well known by epidemiologists, but less understood generally, that the prevalence of a disorder is determined not only by its *incidence* (the rate of new onset of the condition among those at risk) but also by the *duration* of illness after onset. Current knowledge suggests that the age-specific incidence of dementia has changed little over the past decades (Kokmen et al. 1988, 1993), but that is not true for prevalence. Because of increased public awareness and improved medical and (especially) nursing treatments, the typical duration of dementia with onset at a given age has grown substantially. To appreciate this point, one need only contrast the current typical survival of new-onset dementia with data from the seminal Newcastle studies of dementia in the early 1950s by Sir Martin Roth and colleagues. Roth (1955) validated the distinction of dementia from other geropsychiatric disorders by

pointing out that the average duration of dementia after hospitalization was only 2 years. Early studies of dementia in the community found only slightly longer durations of dementia following initial detection (Sturt 1983). Today, the figure is 5–7 years in the United States (Fitzpatrick et al. 2005), and figures are comparable in Europe (Jagger et al. 2000). Paradoxically, this change and our improving abilities to diagnose dementia early have resulted in increased age-specific prevalence of dementia, one of several conundrums in public health cited by the late Ernest Gruenberg (1977) in his classic paper, "The Failures of Success." As a consequence, the well-known estimate by Brookmeyer et al. (1998) of 8–12 million prevalent Alzheimer disease dementia cases in the United States by mid-century may be low.

Further "success" in the mitigation or slowing of dementia symptom progression would surely please the millions of individuals with dementia and their families, because the progressive disability caused by the underlying illness would be curtailed. From a public health perspective, however, such "success" would bring the perverse consequence of a further increase in the survival of those with the disease, resulting in an increase in dementia prevalence. This is only one of several reasons why it is preferable to prevent dementia, or at least to arrest it when affected individuals retain a good proportion of their functional abilities, rather than to treat the condition when it is fully apparent. Increasingly, therefore, randomized trials of interventions for dementia are focused on prevention. Here we consider specifically the prevention of dementia, leaving other aspects of treatment to Chapter 16, "Pharmacological Treatment of Neuropsychiatric Symptoms," Chapter 18, "Pharmacological Treatment of Alzheimer Disease and Mild Cognitive Impairment," and Chapter 19, "Management of Advanced Dementia."

Prevention of Dementia Essentially Means Prevention of Alzheimer Disease

The incidence rates for dementia and Alzheimer disease double with every 5 years of age (Jorm and Jolley 1998). This rule of thumb holds well between ages 60 and 90 years, although less is known about dementia incidence in ages outside this interval (Miech et al. 2002). Less widely appreciated is the variation with age in the proportion of dementia attributable to Alzheimer disease. The percentage of dementia caused by Alzheimer disease is probably about 50% among people in their 60s, but this percentage increases as older age strata are studied. Among those older than age 80 years, the percentage may be as high as 80% (Breteler et al. 1992; Hofman et al. 1991). Presumably, the reason is the dramatic increase in the occurrence of Alzheimer disease with age, whereas other types of dementia are less influenced by age. With the changing age structure of populations in both the developed and (especially) the underdeveloped world (Ferri et al. 2005), a substantial majority of all cases of dementia now fall in the "very old" group whose age exceeds 80 years. Increasingly, therefore, dementia is a result of Alzheimer disease, implying that, to an ever-growing degree, the prevention of dementia requires the prevention of Alzheimer disease.

Chronic Disease Model of Alzheimer Disease

An emerging concept in the past 20 years is that the dementia of Alzheimer disease is only the tip of the iceberg for this disease. Figure 26–1 suggests three continuous phases of AD pathogenesis. The existence of a *latent stage* lasting several decades is indicated by the presence of abundant Alzheimer neuropathology in asymptomatic elderly individuals at least a decade before dementia is apparent (Braak and Braak 1996; Goldman et al. 2001; Price and Morris 1999; Price et al. 2001) and by recent positron emission tomography (PET) findings suggesting significant amyloid deposition in some 20% of cognitively normal elderly (Mintun et al. 2006; Pike et al. 2007).

Other evidence shows suggestive Alzheimer-related changes in asymptomatic individuals who are genetically predisposed to late-life Alzheimer disease (i.e., those with at least one copy of the apolipoprotein E [APOE] ε4 allele). Several studies show that such predisposed individuals have subtle changes on sensitive longitudinal neuropsychological testing years before the diagnosis (Elias et al. 2000; Small et al. 2000; Tierney et al. 1996). Those at risk also show early thinning of medial temporal grey matter (Erkinjuntti et al. 1993; Golomb et al. 1996). Finally, PET studies using fluorodeoxyglucose show regional brain hypometabolism in young individuals at risk, with a pattern similar to that observed in Alzheimer disease (Reiman et al. 1996; Silverman et al. 2001; Small et al. 1995, 2000).

In all, these findings provide powerful evidence that the pathogenesis of Alzheimer disease includes preclinical stages. Because the disease process in these stages has not yet provoked dementia symptoms, at least for Alzheimer dementia, the latent stage of disease should be the ideal time for preventive intervention.

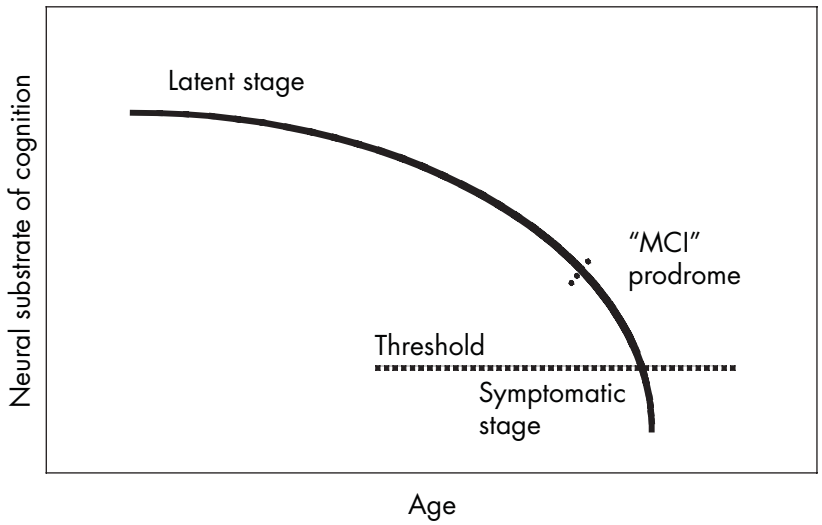

FIGURE 26–1. The progressive development of Alzheimer disease over decades.

Relation of "Normal" Cognitive Aging to Earliest Changes of Alzheimer Disease

A question of long-standing interest is the relation of "latent" Alzheimer pathogenesis to the nearly ubiquitous experience of mild memory loss in individuals who progress from middle age to senescence. It is well known that some decline in ability to learn and retain new information (i.e., in episodic memory) and processing speed is increasingly common with age and, in fact, is evident by middle age (Hultsch et al. 2002; Zelinski and Burnight 1997). Because similar age-related changes in memory and other mental abilities are seen in animal models using both rats and monkeys that do not show the primary hallmarks of Alzheimer pathology, it seems unlikely that all age-related change in cognitive function is the result of Alzheimer pathology. It nevertheless remains possible that groups of individuals with age-related changes in cognition contain two subgroups of individuals: those with "normal" changes in cognition and those whose changes are a very early manifestation of an Alzheimer-type process that is otherwise unapparent (latent). The proportions of people in these two categories are not known, but the plausibility of this perspective in general has increased as the field has come more widely to recognize that Alzheimer disease has an extended latent period (see Figure 26–1). The perspective also becomes more compelling because we now understand that a majority of individuals will develop Alzheimer dementia if they survive long enough (Khachaturian et al. 2004).

If some proportion of "benign senescent forgetfulness" (Kral 1962) proves to be the first blush of an underlying Alzheimer process, the implications will be important. If true, for example, it will increase the importance of finding ways to distinguish between those with "benign" age-related cognitive decline and those who have very early prodromal Alzheimer disease. Doing so would mean that intervention can begin as early as possible. In fact, the failure to recognize the importance of this distinction may have deterred us from more intensive investigation of the earliest pathogenetic events in the Alzheimer process. It may also have deterred us from more aggressive investigation of potential preventive strategies that might be beneficial in middle age or early old age. As effective strategies are developed for the prevention of dementia (mostly Alzheimer disease), it will be important to test also whether these same or similar strategies are useful for the prevention of cognitive decline, at least in some individuals.

Tertiary, Secondary, and Primary Prevention

Figure 26–1 suggests three possible strategies for preventing Alzheimer disease. Because the root causes of the disease are poorly understood, we are probably not positioned today to discuss the prevention of different aspects of the disease process; we are on surer footing, however, when we talk about prevention of Alzheimer *symptoms.* In classical public health parlance, *tertiary prevention* strat-

egies seek to prevent the further progression or complications of symptoms that are already fully evident. *Secondary prevention* can be attempted when the "first blush" of the syndrome (i.e., its prodrome) is evident. The aim of intervention is then delay or avoidance of the full syndrome. *Primary prevention* strategies seek to prevent the emergence of symptoms altogether. In Alzheimer disease, primary prevention of symptoms is theoretically possible during the latent stage of disease. For most people this means intervention in middle age or early senescence.

Most Alzheimer treatment trials have been tertiary prevention trials—that is, they have sought interventions capable of "disease modification" (to use U.S. Food and Drug Administration parlance). This usually means slowing of symptomatic progression or, in a few instances, other evidence of alteration in disease course through, for example, neuroimaging measures. Treatment trials and tertiary prevention are not covered in this chapter but are reviewed in Chapters 16–19.

Secondary Prevention Trials

Secondary prevention trials attempt to enroll people with prodromal Alzheimer disease and then demonstrate the capacity of an intervention to delay the appearance of dementia. A major problem for this approach is that we have no sure method of differentiating prodromal Alzheimer disease from other mild cognitive disorders.

Several criterion-based systems have evolved toward this end, and these vary in their abilities to identify conditions that will evolve within a few years to Alzheimer dementia (or, in current jargon, "convert"). The different criterion-based systems differ in their sensitivity and specificity as predictors of subsequent Alzheimer dementia. The meaning of these terms is depicted in Figure 26–2. In this figure, circle A is small, reflecting the low population prevalence of this condition. Thus, people with such conditions may be difficult to recruit for trials. However, reflecting the high predictive value of its criteria, a substantial proportion of circle A overlaps the target. In studies from the Alzheimer Disease Cooperative Study (ADCS) program of the National Institute on Aging, operationally defined aMCI identified a group of individuals among whom nearly 50% progressed to Alzheimer dementia within 3 years. Restriction of participants to those who possess at least one ε4 allele at the APOE genetic locus would increase this proportion substantially (Petersen et al. 1999). The low rate of "false positives" in circle A (its portions that do not overlap the target circle) indicates that the aMCI criteria also have relatively good specificity (the proportion of all those without the target condition who are identified appropriately by absence of the criteria).

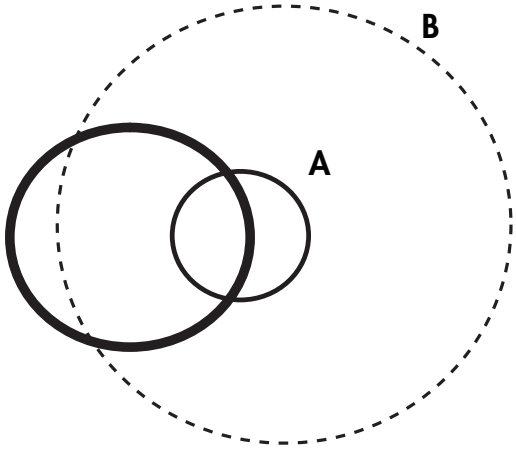

FIGURE 26–2. Implications of strict versus relaxed criteria for mild cognitive impairment.
The figure represents a theoretical population of elderly people. The "target" bold circle represents a set of individuals with "true" prodromal Alzheimer disease, which we define here as those destined to develop Alzheimer dementia over a defined interval of perhaps 3 years. Circle A (solid line) represents conditions such as amnestic mild cognitive impairment (aMCI) as originally defined by Petersen et al. (1999), with high predictive value for the subsequent development of Alzheimer dementia. Circle B (dotted line) represents a set of more relaxed criteria (several are available). Circle B "captures" a large portion of the target circle with true prodromal Alzheimer disease, but also identifies a much larger number of "false-positive" individuals who meet screening criteria but who do not have prodromal Alzheimer disease.

The unfortunate corollary, however, is that screening populations for aMCI or similar conditions will capture only a small portion of individuals with prodromal Alzheimer disease. This is reflected in the figure by the low proportion of the area of the target circle occupied by circle A. In other words, the aMCI criteria have low sensitivity as predictors of subsequent Alzheimer dementia. This problem not only hinders recruitment for secondary prevention trials, as mentioned earlier, but it also provides a relatively select group of trial participants whose results may not generalize well to prodromal Alzheimer disease.

One may avoid the problems of low sensitivity and lack of generalizability by relaxing the entry criteria for secondary prevention trials. The result of this change is suggested in circle B in the figure. Potential participants who meet entry criteria are now more numerous, and they include a much higher proportion of the population's "true" cases of prodromal Alzheimer disease (the target circle), thus providing improved generalizability. The offset is the low predictive value and low specificity of these criteria. When planning trials, these attributes may not be problematic, provided their economic implications (need

for large samples) are adequately recognized. Commonly, however, designers of clinical trials use more optimistic estimates of predictive value (i.e., "conversion" rates), resulting in diminished statistical power.

These issues are exemplified in the four completed trials for secondary prevention of Alzheimer disease (two of which have been published). In a double-masked, three-arm, parallel-design trial of donepezil and high dose vitamin E (Petersen 2005), the ADCS randomized 769 subjects with aMCI and followed them for 3 years for multiple outcomes, notably including development of possible or probable Alzheimer dementia diagnosed using standard criteria (McKhann et al. 1984). Participants were instructed to use no other vitamin preparation. Donepezil was given in the standard dose of 10 mg daily. The annual incidence of new cases of Alzheimer disease averaged 16%, or slightly more than the 12%–15% expected. Given various sources of attrition, over 3 years, 212 participants (27.5% of the original sample) developed Alzheimer dementia, with no apparent differences between placebo- and vitamin E–assigned subjects. Results for the donepezil-treated group were less straightforward but showed a modest trend toward "protection" (hazard ratio = 0.80; 95% confidence interval [CI], 0.57–1.13). However, prespecified analyses at 6-month intervals showed that, compared with the placebo-treated group, those assigned to donepezil had a reduced probability of progression to Alzheimer dementia in the first 12 months (P=0.04), and this finding was also supported by observations on secondary outcome measures. Among those with an APOE ε4 allele, the benefit of donepezil was evident throughout the trial, and a post hoc analysis demonstrated that nearly all of the benefit of donepezil was attributable to its effects in the ε4-positive group (Petersen 2005).

The other published trial tested possible benefits of the selective cyclooxygenase-2 inhibitor rofecoxib (since withdrawn from distribution) for prevention of "conversion" to Alzheimer dementia in aMCI patients (Thal et al. 2005). Although designed similarly to the donepezil/vitamin E trial, this effort used less stringent eligibility criteria for mild cognitive impairment, with the result that the trial cohort's annual incidence of Alzheimer dementia was less than half that observed in the donepezil/vitamin E trial. Because of the resulting slower-than-expected accrual of Alzheimer dementia "events," the trial was extended by 2 years from its planned observation period before it was halted after detection of 189 out of a planned 220 cases of incident Alzheimer disease. The results were disappointing. Although reported as showing no benefit, the trial produced adverse results on its declared primary outcome of incident Alzheimer dementia with a hazard ratio of 1.46 (95% CI, 1.09–1.94). In reporting these results, the authors suggested that the interpretation of this last result should be tempered by a lack of similar adverse results with several secondary outcomes. In addition there are also unpublished trials of galantamine and of rivastigmine. Both of these trials had lower than expected rates of "conversion" to dementia (9% per year and 7% per year, respectively) and did not demonstrate a significant treatment effect.

Problems of Primary Prevention Trials: Cost and Safety

The "crown jewels" of prevention trials are those that attempt to prevent the emergence of Alzheimer symptoms altogether—that is, they are designed to demonstrate efficacy of primary prevention strategies. Most individuals who deal daily with treatment trials, or even with secondary prevention trials, fail to appreciate the enormous cost of such trials. Compounding the cost is the substantial probability of unpleasant surprises that seem have befallen several trials that have attempted to demonstrate primary prevention of Alzheimer disease. A somewhat less costly variant type of primary prevention trial seeks to demonstrate the efficacy of an intervention for the mitigation of age-related cognitive decline.

The problem, both for cost and for untoward events forcing early termination of primary prevention trials, is in the very nature of the trials and the resulting risk-benefit calculus. These trials must enroll several thousand individuals to find a sufficient number of "events" needed for adequate statistical power (a smaller number may suffice for cognitive decline end points). The design may call for a defined period of exposure during which "events" are also counted (typically, with recruitment extending over 1 or 2 years, but with a common ending date for all participants), or it may specify the number of "events" that must occur before the trial is ended. Both approaches depend on an assumed rate of incidence of Alzheimer dementia (or an assumed rate of cognitive decline) in placebo-assigned individuals. Most primary prevention trials to date have been planned with an expected number of about 200 "events" (300 for three-arm, parallel-design trials that test two interventions simultaneously). For a trial with 5 years of average exposure duration and an estimated average Alzheimer dementia incidence rate of 2% per year, about 2,000 participants would be needed to reveal a 30% reduction in dementia incidence, but the actual number is perhaps double this because of deaths and other forms of withdrawal from the trial and because of treatment noncompliance. Furthermore, the observed Alzheimer incidence rate is almost always lower than predicted because of the so-called healthy volunteer effect (some have said, tongue in cheek, that "to

cure a disease, simply enroll all those at risk in a clinical trial"). Most authorities therefore suggest that enrollment of 6,000–8,000 participants is needed for such a trial. With startup time and completion of data-gathering efforts, a "5-year" trial will inevitably require 7–8 years for completion (not counting analysis time), so a trial with 4,000 enrollees will cost more than $50 million, and the costs of a more realistically sized 6,000–8,000 person trial may easily exceed $100 million. Primary prevention trials are expensive!

The other major problem for these trials is their vulnerability to unexpected safety concerns, leading to premature termination of the trial. By definition, primary prevention trials enroll healthy, asymptomatic participants and, from the time of randomization forward, expose them to an intervention. The benefit—if it ever appears—is absence of Alzheimer dementia some years hence; the risks, by contrast, accrue from the day of enrollment. Because there are always risks, it is almost inevitable that trials of strategies for the primary prevention of Alzheimer disease will have an adverse balance of risks versus benefits for several years. The art is in knowing when the accrued risks (in real time) exceed the hoped-for benefits (in the future), discounting the latter in some way for the probability of success in the trial's prevention strategy (Meinert and Breitner 2007). The other clear implication is that the interventions in primary prevention trials must be relatively safe.

As this is written, published trials of strategies for the primary prevention of Alzheimer disease are five in number. Their names are inventive and in some instances hopeful: PREventing Post-menopausal memory loss and Alzheimer's with Replacement Estrogens (PREPARE); PREvention of Alzheimer's Disease by VItamin E and SElenium (PREADVISE); the Women's Health Initiative Memory Study (WHIMS); the Ginkgo Evaluation of Memory (GEM) trial; and the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). All but two of these trials have been stopped owing to concerns about safety that were not anticipated when the trial was initiated. PREPARE and WHIMS were stopped after the large Women's Health Initiative trial of estrogens (conjugated estrogens, equine, either with or without co-administration of medroxyprogesterone acetate) raised concerns about heart disease, stroke, and breast cancer with the treatments. The ADAPT was stopped when new findings elsewhere suggested cardiovascular safety concerns with long-term administration of celecoxib to older people (Solomon et al. 2005), and the ADAPT data suggested that the trial's other treatment (naproxen sodium) may also have similar risks (ADAPT Research Group 2006). PREADVISE continues, as does the GEM study, with results expected in the next year or two. Given recent trials and observational data on vitamin E, however, hopes have declined for a successful outcome of PREADVISE, and there is broad skepticism also about the likely efficacy of the *Ginkgo biloba* extracts being tested in GEM. One hopes that such skepticism is unwarranted, but overall, the lessons of these trials seem clear. The field initially underestimated both the cost and the safety risks in Alzheimer primary prevention trials. As a result, attention is now turning to interventions such as exercise and dietary interventions with reduced risks and with expected collateral health benefits. There is limited animal and epidemiological evidence to suggest that these interventions may be helpful in preventing Alzheimer dementia (as discussed later in this chapter). Another approach may lie in the development of adequate "biomarkers" of disease progression in the latent or prodromal stage, with hopes that these may be more precise and more sensitive indicators of disease pathogenesis than is the Alzheimer dementia phenotype itself. There are examples of successful development of such "biomarkers" as surrogate end points in trials (CD4 counts and viral load in HIV/AIDS trials being a notable example), but there are also many pitfalls (Fleming and DeMets 1996).

The Alternative Is Observational Evidence

Because there is very little current evidence for Alzheimer dementia prevention strategies from randomized, controlled trials, we turn to a lesser form of evidence, so-called observational studies. These are *not* experiments in the usual sense because the investigator does not alter the milieu or condition of anyone or anything. Instead, differences in people's circumstances and their individual choices are used to create groups that are nonrandomly exposed to various conditions, and then to examine the association of those conditions with the occurrence of Alzheimer dementia or cognitive decline. This sort of design can demonstrate association but not causality. The reason is simple enough: individuals who are relegated by circumstance or choice to different exposure groups are not necessarily similar. Instead, they may differ in characteristics that are related not only to their exposure status but also to their disease status. This phenomenon is called *confounding,* and the factors that are associated with both exposure status and outcome are called *confounders.* These terms are widely misused; they have specific meanings that do not equate to imprecise or "noisy" data or to invalid measures of exposure or outcome (which may produce other sorts of bias).

Epidemiologists who conduct observational studies often attempt to control confounding by "adjusting" for confounders in their analyses. This is a useful approach that can substantially improve the inference from their studies. However, it has two important limitations. First, it is sometimes impossible to measure fully the confounding factor. Consider socioeconomic status, which often brings differences in lifestyle variables that range from health-related habits (e.g., smoking) to access to medical care and preventive health practices (e.g., mammograms, colonoscopies, frequent measures of prostate-specific antigen). Socioeconomic status is a complex trait that is difficult to measure. Various surrogate measures are available, ranging from educational attainment to income level to occupational complexity or prestige, but none of these fully captures the underlying trait. The unmeasured residue may still result in exposure-outcome associations that are false *(residual confounding).* An example is provided in the epidemiological studies of postmenopausal hormone replacement and cardiovascular disease. Early studies incorporated only crude attempts to control for socioeconomic status, and these showed an association between hormone use and reduced morbidity from cardiovascular disease. More recent studies have used improved methods of controlling for socioeconomic status, and the "protective" association has disappeared (Colditz 2003; Nelson et al. 2002).

The other way that confounding may lead to deceptive results in observational studies—even those with excellent measures of known confounders—is the influence of unsuspected or unknown confounders. Because they are unsuspected, they are not measured, and one cannot adjust for characteristics that are unmeasured.

These sorts of problems with measurement of exposure and with confounding relegate observational studies to a second-choice status in comparison to randomized, controlled trials, even though the latter are difficult and time consuming. This fact led Donald Fredrickson (1968), Director of the National Institutes of Health from 1975 to 1981, to characterize large field trials as "the indispensible ordeal," noting that they prolong the moment of truth to excruciating limits, but also concluding, "If, in major medical dilemmas, the alternative is to pay the cost of perpetual uncertainty, have we really any choice?" The question is surely apt for investigation strategies for prevention of dementia. The difficulties facing prevention trials are better understood than they once were, but "have we really any choice?"

Risk Factors for Investigation

More and better prevention trials are urgently needed, but until we have good data from trials, observational study data are all we have. As long as they are not overinterpreted, well-conducted epidemiological studies can be of great value. They can identify variables that may not have been anticipated (e.g., the association between increased physical activity and maintenance of cognition). They can also identify variables that can be examined in animal models, both to determine the underlying neurobiology and to conduct clinical trials in animal models. Thus, ultimately they may identify variables that can be used in clinical trials in humans.

Their general nature—investigating the association between "exposure" and a defined outcome—leads observational studies as a matter of course to the identification of characteristics that predict or presage the development of a disease or the lack of this disease where unexposed individuals show it more frequently. These variables are termed *risk factors* or, when appropriate, *protection factors,* and they can be very important. Consider, for example, the role of risk factor identification as a precondition to the striking decline in cardiovascular morbidity and mortality in the developed world since the 1950s. This decline started long before the availability of trials data to show the benefits of aspirin, lipid-lowering drugs, or even antihypertensive drugs. Beginning with the Framingham study in the late 1940s, observational data demonstrated strong relationships between any of several factors and cardiac disease. In the 1950s and 1960s additional observational studies confirmed these risk factors. In those years, the field of cardiovascular medicine became increasingly convinced of the potential benefits of risk factor modification. At the same time, public awareness of the risk factors grew, and populations in the developed world changed their diet and, to a limited extent, their behavior. Only in the 1970s, 1980s, and 1990s—long after the identification of the risk factors—did important results from randomized trials show proof that effective risk factor modification would result in improved health outcomes.

The cardiovascular risk factor modification story also shows how all risk or protective factors are not created equal. There is an important dichotomy between those that are amenable to intervention and others that (for now at least) are not. Examples of the latter in the dementia field are age and genetic predisposition. Aging increases the risk for dementia (it doubles every 5 years), but what is the alternative? Likewise, after controlling for age, genes may predict as much as 75% of the variability in susceptibility to Alzheimer dementia (Pedersen et al. 2004). What are we to do then: "choose our parents wisely?"

As risk factors are first identified by observational studies, how much credence should we put in these findings? Although never a substitute for an "evidence base" from randomized trials, epidemiological studies of risk

factors have improved dramatically in quality over recent decades. In that time, several trials have addressed questions for which previous observational studies had already suggested a likely outcome. In the large majority of instances, trial results have confirmed those from well-controlled observational studies (Concato and Horwitz 2004). When trial and observational results are in disagreement, the first question should be whether there are obvious methodological shortcomings in the observational studies (or, for that matter, the trials—although this is less common). An important second concern is whether the observational study and the trial have addressed the same question. Trials, with their typical time horizon of a few years, cannot assess longer-term associations of antecedents to outcomes. For example, considerable observational data have suggested that postmenopausal hormone replacement therapy (HRT) may protect against dementia. Most often, the HRT exposures have been initiated in middle life at or near the time of menopause. In many instances, they have been continued for a limited time and then terminated in late middle-age or early senescence. By contrast, the women who developed dementia in the Women's Health Initiative, and its ancillary evaluations of cognition, were much older when enrolled in the trial (Shumaker et al. 2004). Compared with perimenopausal use, initiation of HRT at age 65, 70, or 75 years may have quite different results. Thus, the surprising adverse results of the WHIMS may reflect a difference in timing of exposure more than any error in the observational data. Recent analyses in the Women's Health Initiative trials (not WHIMS) have suggested that such timing issues are important in analyses of cardiovascular outcomes (Manson and Bassuk 2007), and at least one observational study of HRT and dementia risk suggested very different outcomes for HRT exposures in middle versus later life (Breitner and Zandi 2003; Zandi et al. 2002b).

Lifestyle Factors

Among the most attractive candidate interventions for prevention of dementia are those that alter "lifestyle" choices in health habits, diet, exercise, and the like. The strength of this approach is that most such changes are thought to improve many health outcomes other than dementia, so they are likely not only to be safe but also to be beneficial. The weakness is that it is difficult to bring about societal changes in such health-related behaviors and choices. Change is not impossible, however, as is evidenced by the success of the public health campaign against smoking in decreasing U.S. tobacco use with its attendant risks for cardiovascular, pulmonary, and neoplastic diseases, or by other changes in diet and "lifestyle" factors that are demonstrably important as predictors of atherosclerotic cardiovascular disease.

If behavioral and lifestyle factors are important determinants of dementia risk, then these may also represent important potential avenues to prevention of dementia and cognitive decline. This idea has primarily been examined through epidemiological studies of community-dwelling individuals selected as representative samples of the population who were high functioning. These studies typically assessed a wide variety of factors, and the subjects were then reevaluated after several years. The analyses have examined factors predicting maintenance of cognition over time, risk of dementia in general, or risk of Alzheimer disease in particular.

The first of these studies (Albert et al. 1995) examined individuals who were already elderly (i.e., age 70–80 years), looking at predictors of maintenance of cognitive function over a 3-year span of time. Many subsequent reports, however, have been based on individuals who were assessed in middle age and were then followed for decades into old age (Karp et al. 2006). This latter approach is preferable because it reduces the likelihood that the pathological processes responsible for the cognitive decline (e.g., Alzheimer disease) might have already begun at the time of the first evaluation and thereby influenced behavior in subtle ways, even though the participants appeared to be asymptomatic. In addition, subsequent reports have included subjects who had widely varying ethnic and cultural backgrounds and who lived in both urban and rural settings (Albert et al. 1995; Laurin et al. 2001; Rovio et al. 2005; Scarmeas et al. 2001; Schmand et al. 1997; Weuve et al. 2004; Wilson et al. 2003). This fact reduces the likelihood that factors unrelated to the variables of interest are responsible for the findings. It is also notable that these studies used a wide range of cognitive measures as outcomes; some have examined composite scores based on a comprehensive neuropsychological battery, whereas others have looked primarily at selected areas of cognition, such as memory. The results appear to be reasonably robust and to transcend one particular cognitive domain.

A panel of scientists recently convened by three of the institutes at the National Institutes of Health (National Institute on Aging, National Institute of Neurological Disorders and Stroke, National Institute of Mental Health) reviewed the existing literature and issued a white paper on their findings (Hendrie et al. 2006). The review concluded that there were four independent factors (apart from genetics) that appear to be consistently predictive of maintenance of cognitive function: 1) increased levels of physical activity, 2) increased levels of mental activity, 3) increased social engagement, and 4) control of vascular risk factors. In addition, the data suggest that the benefit

gained from each of these independent lifestyle interventions provides an added benefit in that risk of cognitive decline is incrementally reduced with the addition of two or more of these factors (Karp et al. 2006).

These reports have prompted a number of researchers to examine the mechanisms by which such lifestyle factors might directly benefit brain function. This question has most effectively been studied by the use of animal models, because these models can disentangle the issue of innate differences during life from differences based on experience and, at the same time, address the issue of the underlying brain mechanisms that may be involved. The study design most commonly employed is to examine changes in brain function, as well as cognition, in groups of animals prior to and after exposure to an environmental manipulation and to compare these measures with those from animals with no environmental manipulation. The animals most commonly used in these studies have been rats or mice, and cognitive performance has most often been assessed by measuring memory performance in the Morris Water Maze (Morris 1984). In these studies, genetics can be controlled by dividing littermates into experimental and control groups.

The following section reviews findings from at least three sources related to this issue: 1) epidemiological studies that have identified risk factors of interest, 2) studies using animal models in order to understand the brain mechanisms that might be involved, and 3) controlled clinical trials, where they exist.

Physical activity

Epidemiological studies have typically examined physical activity by obtaining information about the types of physical activity that individuals engage in during the course of daily life (e.g., walking, climbing stairs). Participants are typically asked to indicate the duration and frequency of such activities. This information is then used to generate a measure of total kilocalories expended, adjusted for potentially confounding factors (e.g., comorbid conditions, physical limitations, smoking). Many epidemiological studies have now reported that increased levels of physical activity are associated with maintenance of cognitive function (Albert et al. 1995; Laurin et al. 2001; Weuve et al. 2004) as well as delay in the onset of Alzheimer disease (Abbott et al. 2004; Podewils et al. 2005; Rovio et al. 2005).

The animal model that has been used to examine these findings further is known as the *voluntary exercise paradigm.* In this paradigm, a running wheel is made available to animals for short periods (e.g., 4 weeks) or long periods of time (e.g., 5 months), with measurements of brain function and cognition compared in those with exposure to the exercise paradigm versus those without. Several consistent findings have emerged from these investigations: 1) exercise enhances learning in the water maze for both young animals (Berchtold et al. 2002) and old animals (van Praag et al. 2005); 2) exercise enhances mRNA expression of brain-derived neurotrophic factor in at least one subregion of the hippocampus (the dentate gyrus) (Berchtold et al. 2002; Farmer et al. 2004); and 3) exercise enhances neurogenesis in the hippocampus (Brown et al. 2003). It is noteworthy that, although neurogenesis is known to occur in young and old animals in both the hippocampus and the olfactory bulb, the increase in neurogenesis following exercise occurs only in the hippocampus. Increases in brain-derived neurotrophic factor expression likely serve to increase synaptic plasticity in nerve cells, whereas neurogenesis provides an increased supply of nerve cells in a brain region essential for normal memory.

Investigators are currently examining the effects of varying factors such as frequency, duration, and age of exposure to exercise in order to determine the specific aspects of physical activity that might be most beneficial, as well as to demonstrate more convincingly a causal relationship between physical activity and cognition, rather than just an association. For reviews of these issues see Cotman and Berchtold (2002), Cotman et al. (2007), and Dishman et al. (2006).

The consistency of the findings relating physical activity to cognitive function has led some investigators to conduct small clinical trials in humans. These studies have involved randomizing participants to a physical activity program versus an educational program and measuring change in cognition and/or change in imaging markers of the brain. The results have shown that cognition is better among individuals who have participated in an exercise program compared with individuals who have not (Colcombe et al. 2004). Moreover, measures of differences in brain structure and function parallel these cognitive changes (Colcombe et al. 2003; Erickson et al. 2007; Hillman et al. 2004). For example, it has been shown that exposing older individuals to a 6-month program of aerobic activity enhances performance on neuropsychological tasks (e.g., attention and executive functions) and increases brain activation during a functional magnetic resonance imaging task requiring complex attention (Erickson et al. 2007).

Mental activity

The earliest findings from epidemiological studies explored predictors of maintenance of cognition. Many studies reported that increased levels of education were associated with a greater likelihood of maintaining cognitive function over time (Evans et al. 1993; Farmer et al. 1995) as well as a lower likelihood of developing dementia

(Dartigues et al. 1991; Fratiglioni et al. 1991; Korczyn et al. 1991; Rocca et al. 1990; Schmand et al. 1997; Sulkava et al. 1985; Zhang et al. 1990). More recent studies have tried to determine whether the association with education comes only from early exposure to education, or whether more extensive education is a surrogate indicator for a tendency to engage in mentally stimulating activities over a lifetime. To evaluate this question, numerous studies have now evaluated the range of mental activities in which a participant might be involved (e.g., reading books, going to lectures, playing board games). Investigators then typically examine the total hours spent doing these activities, adjusting for potential confounders. A range of recent studies have reported that increased time committed to cognitively stimulating activities is associated with lower risk of cognitive decline and dementia (Hultsch et al. 1999; Scarmeas et al. 2001; Verghese et al. 2003; Wilson et al. 2002, 2003, 2007c). These findings suggest that education may instill lifelong habits of mental stimulation that produce alterations in the brain. In this manner, the effect of education on brain function would be mediated by habits that were maintained throughout life.

There are several other possible explanations for the association between increased education and decreased risk of cognitive decline. Education may reflect environmental factors that are more likely to occur among people with less education (e.g., poor diet or head injury) and may lead to alterations in brain development or produce a vulnerability to disease late in life. Educational attainment may also be a surrogate for native intellect (Plassman et al. 1995), which alters an individual's ability to perform well on tests of cognitive function and thereby masks a true decline. Finally, education may produce direct effects on brain structure by, for example, producing an increase in synapse number or vascularization (Diamond et al. 1985; Greenough et al. 1985). Longitudinal studies reduce the likelihood that the first two explanations are correct, but they cannot completely eliminate them as possibilities.

The primary clinical trial data pertaining to the impact of mental activity on maintenance of cognition come from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial. This was a multicenter study in which older individuals were randomized to training that focused on three different cognitive domains (memory, reasoning, and speed of processing) as compared with a control condition. The cognitive training produced improved function, even after a duration of 5 years, but this improvement was largely specific to the cognitive domain involved (Willis et al. 2006). There was also an indication that reasoning training reduced functional decline 5 years later, but to date this finding has been based on self-report.

Animal models have also been used to examine the effect of mental activity on cognitive decline. The paradigm most commonly used to mimic mental activity is known as the *enriched environment strategy* (Hebb 1947). In the current version of this paradigm, the enriched environment is an animal cage in which have been placed many objects that the animal can explore. As with the voluntary running wheel described earlier, duration of exposure can be varied, as can degree of stimulation, by changing the objects at varying frequencies and/or by altering the number of animals in a cage at the same time. The two consistent findings that have emerged from this work are that an enriched environment enhances learning in the water maze (Kempermann et al. 1997), and an enriched environment enhances hippocampal neurogenesis but not neurogenesis in the olfactory bulb (Brown et al. 2003). There are also reports of increased expression of growth factors, such as nerve growth factor (Pham et al. 1999), but these findings have been less widely replicated.

The interpretation of these findings remains unclear, because investigators have not disentangled the effects of increased exercise in the enriched environment from those of mental enrichment. There have, in fact, been few direct comparisons of enrichment versus exercise. One potential approach would be to determine if the benefits are additive—that is, whether exposure to an enriched environment after exposure to exercise alone provides a greater change in the outcome measures than either intervention alone. It would also be helpful to find greater change in the brain following both interventions than with one alone (see van Praag et al. 2000 for a review of this issue). Difficulty with interpretation of the animal data increases the challenge of interpreting the human findings as well. It has been hypothesized that mentally stimulating activity by any of the mechanisms described here may permit compensation for age-related declines and thereby provide cognitive reserve (Scarmeas and Stern 2004). An alternative hypothesis is that mental activity has a direct impact on Alzheimer pathology.

Other animal models have been used to help address the latter issue. Relevant studies have used transgenic mice containing genetic mutations known to cause Alzheimer disease in humans. These transgenic mice produce plaques similar to those seen in AD, which contain the amyloid beta (Aβ) protein. Moreover, as the animals age, they develop memory problems above and beyond those seen by their littermates without the genetic mutations. Several studies have now examined whether exposure to an enriched environment improves memory in these transgenic animals and alters amyloid load. The studies that have examined cognition consistently find that memory performance is improved in the mice ex-

posed to an enriched environment, but the studies differ with regard to whether amyloid burden also decreases. Some studies report reduced levels of Aβ (Adlard et al. 2005; Lazarov et al. 2005); some report that levels of Aβ are stable (Arendash et al. 2004); and some report increased amounts of Aβ (Jankowsky et al. 2005). Much more work is needed to identify the methodological differences that contribute to these varying results.

Finally, the relationship between lifestyle factors, cognition, and severity of Alzheimer pathology in humans has been examined in a small number of recent studies. The findings suggest that level of education modifies the association of amyloid load with cognitive performance (Bennett et al. 2005). These findings need to be expanded in order to be fully understood.

Social engagement

Many epidemiological studies have reported that some aspect of social function is related to maintenance of cognition (Albert et al. 1995; Barnes et al. 2004; Holtzman et al. 2004; Seeman et al. 2001; Singh-Manoux et al. 2003; Smits et al. 1995; Zunzunegui et al. 2003) or delayed onset of Alzheimer disease (Karp et al. 2006; Saczynski et al. 2006). Studies have differed widely, however, on the specific aspect of social function they have measured. The measures have included assessment of social networks, feelings of self-efficacy, and feelings of self-worth. Collectively, these measures are often referred to as assessments of "social engagement."

The neurobiological explanation for these findings remains unclear. The hypothesis most frequently proposed is that increased social engagement serves to buffer the effects of the stressors that occur in daily life and may therefore modify the impact of stress hormones on brain function. To address this issue, a number of recent epidemiological studies have attempted to measure stress-related behavior directly. For example, distress proneness has been associated with a faster rate of cognitive decline over time (Wilson et al. 2005), with the development of incident mild cognitive impairment (Wilson et al. 2007d), and with an increased likelihood of developing dementia (Wilson et al. 2007a). Likewise, loneliness has also been associated with an increased risk of Alzheimer disease (Wilson et al. 2007b). In all of these studies, the effects appear to be independent of measures of Alzheimer neuropathology (but not necessarily to other anatomic changes in brain). The authors of these reports have therefore suggested that the primary underlying mechanism for the association between social factors and cognitive performance pertains to the impact of stress on brain function.

Additional evidence for this mechanism comes from several related sources. Psychiatric conditions, such as major depression, have been associated with atrophy of the hippocampus and other interconnected brain regions (Drevets et al. 1997; Sheline et al. 1996), and it has been proposed that chronic psychological stress is similar to depression and has a direct impact on the brain that would make it more vulnerable to alterations in structure and function. Numerous studies in animals have examined the impact of stress hormones on brain structure and function. For example, increased glucocorticoid levels in the brain alter spatial memory, synaptic plasticity, and hippocampal volume (Bodnoff et al. 1995). However, animal models that have attempted behaviorally to mimic a stressful environment have, to date, been limited and not entirely satisfactory. For example, restraining the movement of an animal for varying periods of time impairs memory performance (Conrad et al. 1996), but physical restraint does not appear to be a good model for the type of chronic stress people feel in daily life. There is as yet no animal model that establishes a firm connection between increased periods of stress, elevation of glucocorticoids, and damage to neuronal function (for a review of these issues, see Sapolsky 2003).

Cardiovascular fitness

It is increasingly clear that vascular pathology plays a major role in cognitive decline among older persons. This conclusion is based on findings that include the observation that individuals with multiple vascular risks are more likely to show cognitive deficits than individuals without such risk factors. Furthermore, the presence of vascular risk factors increases the likelihood that an individual will develop Alzheimer disease. In addition, the severity of cognitive symptoms in persons with Alzheimer disease is exacerbated by the coexistence of vascular risk factors, and finally, the severity of the brain alterations associated with Alzheimer disease is also increased by the co-occurrence of vascular risk factors.

Vascular risk factors for dementia and cognitive decline include hypertension, hypercholesterolemia, presence of diabetes, presence of heart disease, and current smoking. Older individuals with multiple vascular risks have poorer cognitive function than healthy control subjects (Elkins et al. 2004; Knopman et al. 2001; Piguet et al. 2003; Saxton et al. 2000; Selnes et al. 2005; Xiong et al. 2006). Individuals with evidence of vascular risk factors are also at greatest risk for cognitive decline (Elias et al. 2004; Grodstein et al. 2001; Peila et al. 2006; Qiu et al. 2005; Swan et al. 1998; Whitmer et al. 2005; Yaffe et al. 2004, 2007). Consistent with these findings, the risk for Alzheimer disease is increased with the number of vascular risk factors present (Luchsinger et al. 2005; Newman et al. 2005). When the relative contribution of each of these risk factors

is evaluated, the presence of diabetes appears to contribute most to the risk for the development of Alzheimer disease (Muller et al. 2007; Ott et al. 1999). The presence of diabetes is also related to a significantly higher risk of cognitive decline (Arvanitakis et al. 2006) and the development of mild cognitive impairment (Luchsinger et al. 2007).

In vivo imaging studies have also indicated that the hallmarks of vascular disease on magnetic resonance imaging are associated with cognitive decline and dementia. Cerebral white matter lesions are associated with poorer performance on cognitive testing (de Groot et al. 2000). Individuals with silent brain infarcts have a steeper decline in cognitive function and a greater risk of developing dementia than those without these abnormalities (Vermeer et al. 2003). Increased atrophy of regions within the medial temporal lobe is associated with increased cognitive decline, and rapidity of cognitive decline is increased when evidence of brain vascular disease is also present (de Leeuw et al. 2006; Rosano et al. 2007). Likewise, coexistent vascular risk factors increase the atrophy rate of medial temporal lobe regions (Carmichael et al. 2007; Korf et al. 2007).

Likewise, pathological findings demonstrate that vascular disease has an impact on cognition, even when the presumed primary cause of cognitive impairment is Alzheimer disease. For example, two recent studies have demonstrated that dementia severity among individuals with substantial Alzheimer pathology is greater when vascular pathology is also present (Chui et al. 2006; Schneider et al. 2004). This is particularly important because recent autopsy series have now shown that vascular pathology is common in aging brains. Although pure vascular dementia is quite rare (Jellinger 2002; Nolan et al. 1998), vascular pathology in combination with Alzheimer pathology is common (Jicha et al. 2006; Launer et al. 2007; Schneider et al. 2007). An important recent finding is that the frequency of "microvascular infarcts" at brain autopsy is almost as strongly associated with antemortem dementia status as is neurofibrillary tangle score (Sonnen et al. 2007).

Animal models of individual vascular risk factors have confirmed the association between vascular risk factors and cognitive decline. For example, a monkey model of hypertension using surgical coarctation of the midthoracic aorta to produce sustained hypertension results in changes in monoamine receptors in the prefrontal cortex as well as deficits on cognitive testing. (Moore et al. 2003, 2005). Comparable findings have been produced by studies of the spontaneous hypertensive rodent (Watanabe et al. 1997) and animal models of diabetes (Frode and Medeiros 2008).

Though these findings are quite consistent and have been replicated by numerous independent groups, the primary limitation in making specific recommendations to the general public regarding vascular risks is that human data from controlled clinical trials are limited. Several trials have probed the effect of blood pressure reduction on cognitive decline. At least three large clinical trials have been completed, representing a total of more than 12,000 individuals: the Systolic Hypertension in the Elderly Prevention trial (Di Bari et al. 2001); the United Kingdom Medical Research Council trial (Prince et al. 1996); and the Systolic Hypertension in Europe trial (Forette et al. 1998). A Cochrane meta-analysis that examined the results of these studies reported that reducing blood pressure produced an 11% reduction in relative risk for dementia in patients with no previous evidence of cerebrovascular disease, but this was not statistically significant (McGuinness et al. 2006). The authors of the Cochrane review suggested that these results be viewed cautiously because a large number of subjects randomized to placebo were started on antihypertensive medication prior to the end of the trial, and many subjects were lost to follow-up. Furthermore, it is not clear whether the cognitive effects of antihypertensive medicines are attributable solely to their effect on blood pressure or whether they may act by other mechanisms. Limited length of treatments may also have influenced the results, because epidemiological data suggest that the duration of antihypertensive treatment affects the outcome of reduced risk for dementia and cognitive decline (Peila et al. 2006). In addition, no randomized trial has treated more than one vascular risk factor at the same time. Clearly, more randomized trials are needed in order to determine the likely benefit to cognition from treatment of vascular risks.

Diet and nutritional supplements

Dietary patterns have also been associated with lowering risk for cognitive decline and dementia. There are a number of studies that suggest that intake of certain types of fat is related to lowering rate of cognitive decline and risk for incident of Alzheimer disease. One of the first findings showed that individuals who consumed fish at least once per week experienced a 60% reduction in risk for Alzheimer disease (Morris et al. 2003a) as well as a slower rate of cognitive decline (Morris et al. 2005). The relationship between fat intake (both saturated and trans-unsaturated fat) and cognitive decline appears to be linear (Morris et al. 2004), and both a high intake of copper and a high intake of saturated and trans fats may act synergistically to produce an increased rate of cognitive decline (Morris et al. 2006). By contrast, total intake of n-3 polyunsaturated fatty acids may be associated with a reduced risk of Alzheimer disease (Morris et al. 2003b). Data from animal models suggest that the effect of fat intake may be related not only to its influence on vascular risks but also to a di-

rect effect of polyunsaturated fatty acids on accumulation of Aβ (Sahlin et al. 2007).

Other evidence suggests that the so-called Mediterranean diet is associated with a lower risk for Alzheimer disease (Scarmeas et al. 2006b) and a lower mortality once the disease is established (Scarmeas et al. 2007). One hypothesis for this relationship is that the Mediterranean diet lowers vascular risks, but a recent analysis suggests this is not the case (Scarmeas et al. 2006a). The inclusion of vascular risks in multiple logistic regression models suggested independent effects of vascular risk factors (presence of hypertension, diabetes, stroke, heart disease, lipid levels) and other relevant covariates (caloric intake, smoking, and body mass index) on the magnitude of association between the Mediterranean diet and risk for Alzheimer disease. The authors hypothesized that other biological factors (e.g., oxidative, inflammatory) are likely responsible but acknowledged that there could be error in measuring vascular risk in such a study. Further exploration of this issue is needed.

Related to type of diet is food content of antioxidant vitamins C and E. Antioxidants scavenge free radicals and other reactive oxygen species that damage cellular membranes, organelles, and macromolecules. Accumulation of reactive oxygen species may overwhelm the protective reserves of antioxidants in cells (so-called oxidative stress). In neurons, which are especially vulnerable to free radical–mediated damage, these processes may be important in aging of the brain and the pathogenesis of Alzheimer disease (Behl 1999). Thus, antioxidants in the diet or, more powerfully, in nutritional supplements, are candidate neuroprotective agents (Grundman 2000; Henderson 1988). Indeed, three prospective observational studies found lower risks of dementia or Alzheimer disease in participants consuming increased amounts of dietary antioxidants (Commenges et al. 2000; Engelhart and Breteler 2002; Morris et al. 2002).

Because judicious doses of antioxidant vitamin supplements are relatively nontoxic and may have wide-ranging health benefits, such supplements could offer an attractive prevention strategy. An early study of 633 participants found no incident Alzheimer cases over 4 years among individuals who reported use of vitamin E or C supplements at baseline (Morris et al. 1998), whereas an investigation of 3,385 men found reduced prevalence of vascular and mixed dementias, but not Alzheimer disease, among users of both vitamin E and C supplements (Masaki et al. 2000). These results contrast with a recent study showing no association between Alzheimer disease and antioxidant vitamin consumption in either dietary or supplement form (Luchsinger et al. 2003). A randomized, controlled trial showed that selegiline or high-dose vitamin E supplementation may slow the progression of Alzheimer disease (Sano et al. 1997), but assignment to a vitamin E intervention group in the United Kingdom Heart Protection Study (MRC/BHF Heart Protection Study 2002) resulted in no detectable difference in telephone cognitive screening scores at trial termination, and a trial regimen of high-dose vitamin E alone (no vitamin C was allowed) was not effective in delaying the "conversion" of mild cognitive impairment to Alzheimer disease (Petersen 2005).

A possible explanation for some of the discord in these findings may be offered by a study of 3,227 seniors of both sexes that showed significantly reduced prevalence and incidence of Alzheimer disease in participants who used both vitamin E and C supplements, but not in those using either supplement alone (Zandi et al. 2004)—a finding that echoes studies relating cerebrospinal fluid biomarkers of Alzheimer pathogenesis to antioxidant supplement use in patients with mild Alzheimer disease (Quinn et al. 2004). The benefits of combined water-soluble vitamin C and lipid-soluble vitamin E antioxidant interventions should be investigated further.

Pharmaceutical Prevention Strategies

Given our meager understanding of the pathogenesis of Alzheimer dementia, the development of rational pharmacological therapies or prevention strategies is still some distance off. In the meantime, as with other interventions, a sizeable body of observational evidence has accrued to suggest that several categories of common medicines may modify the risk of Alzheimer disease. All these medicines are approved for other clinical applications and are believed to be safe when used by adult populations for a limited time. A number are available in the United States without prescription. However, none of these drug classes has been adequately tested for safety when given to very old populations for periods of years—as would likely be necessary for efficacy in primary or even secondary prevention of Alzheimer disease.

Nonsteroidal anti-inflammatory drugs

Initial interest in inflammation and anti-inflammatory treatments for Alzheimer disease was spurred by laboratory findings of immune activation in Alzheimer disease brains (McGeer et al. 1989) and by the observation of a lower-than-expected frequency of Alzheimer disease in patients coming to autopsy with clinical diagnoses of rheumatoid arthritis (believed at the time to have been nearly obligate users of nonsteroidal anti-inflammatory drugs [NSAIDs]) (McGeer et al. 1990). These findings were followed by encouraging results from a pilot clinical trial of indomethacin for treatment of Alzheimer disease (Rogers et al. 1993) and early observational study results

showing an inverse association of Alzheimer disease onset with severe inflammatory joint disease (Breitner et al. 1994) and with use of NSAIDs (Breitner et al. 1995). In the ensuing 10 years, more than 30 observational studies addressed the possibility that NSAID use is inversely associated with Alzheimer disease incidence, and two recent meta-analyses have confirmed this association (Etminan et al. 2003; Szekely et al. 2004), suggesting very strong protection among those who had used NSAIDs for more than 2 years prior to Alzheimer disease onset (Etminan et al. 2003). It is probably worth noting that none of the published relevant observational studies reported evidence for protection when NSAID use was less than 2 years before dementia onset, and two studies specifically suggested an absence of such a near-term effect of NSAIDs (in 't Veld et al. 1998; Zandi et al. 2002a). We should also note observational studies that have investigated the efficacy of NSAID use for the prevention of age-related cognitive decline, a possible early prodromal change in Alzheimer dementia. One of these found an effect that appeared to be specific for participants who bore one or more copies of the APOE ε4 allele and whose cognitive decline might therefore be more specifically indicative of prodromal Alzheimer disease (Hayden et al. 2007).

A limited literature on NSAIDs in laboratory and animal models also supports the possibility that the drugs may protect against Alzheimer disease pathogenesis (see, for example, review by Cole et al. 2004). In Alzheimer transgenic mice, a sustained diet including ibuprofen resulted in reduced amyloid plaque formation and attenuation of the cognitive decline that otherwise accompanies aging in these animals (Lim et al. 2001). In another series of experiments, certain NSAIDs (but not others) were shown to modulate γ-secretase activity away from production of amyloidogenic $A\beta_{42}$ peptide and toward the less toxic $A\beta_{40}$. However, the latter Aβ-centric hypothesis regarding mechanisms of NSAIDs has not been sustained in a large meta-analysis of six North American cohort studies of NSAID use and Alzheimer disease (Szekely et al. 2008).

Apart from the aforementioned pilot trial of indomethacin for treatment of Alzheimer disease, there have been seven other treatment trials of NSAIDs (Aisen et al. 2002, 2003; Reines et al. 2004; Scharf et al. 1999; Soininen et al. 2007) or other anti-inflammatory strategies, including low-dose corticosteroids (Aisen et al. 2000) and hydroxychloroquine (van Gool et al. 2001). The most important of the NSAID trials, conducted by the ADCS, was a three-arm, parallel-design trial that tested rofecoxib and naproxen against placebo for mitigation of progression in cognitive outcomes (Aisen et al. 2003). Although power was sufficient to demonstrate moderate but important effect sizes, neither of the interventions resulted in any benefit. In fact, there was a trend toward adverse effects in the group assigned to rofecoxib. Two of the other trials examined possible benefits of selective cyclooxygenase-2 inhibitors but found no benefit with either rofecoxib (Reines et al. 2004) or celecoxib (Soininen et al. 2007). As we note elsewhere, a secondary prevention trial using rofecoxib for prevention of "conversion" from mild cognitive impairment to Alzheimer dementia found no benefit but rather a suggestion of harm in the treated group (Thal et al. 2005).

To date, only one trial has attempted to demonstrate efficacy and safety of long-term NSAID use for the primary prevention of Alzheimer disease. Treatments in the ADAPT study were stopped after an average 2 years of treatments because of cardiovascular safety concerns about both its treatments: celecoxib (safety results reported from other trials) and naproxen (based in part on ADAPT safety data) (ADAPT Research Group 2006). Analysis of treatment efficacy was disappointing: after an average 2 years assigned to treatments, both the celecoxib and naproxen groups showed no reduction in incidence of Alzheimer disease dementia, and a suggestion of increased risks (ADAPT Research Group 2007).

Statins

The 3-hydroxy-methyl-glutaryl-CoA reductase inhibitors (statins) are increasingly popular drugs for cardiovascular indications, and it is thought they may also have protective effects against dementing illness. Statins are effective treatments for hypercholesterolemia, a possible risk factor for both vascular dementia (Moroney et al. 1999) and Alzheimer disease (Kivipelto et al. 2001; Notkola et al. 1998). Hypercholesterolemia is associated with vascular disorders, including atherosclerosis, that may confer increased risk for dementia (Hofman et al. 1997).

At least six case-control studies have examined the association between statin use and risk of dementing illness. A nested case-control study from the United Kingdom–based General Practice Research Database (Jick et al. 2000) showed reduced risk of dementia among those with prior use of statins but not other lipid-lowering agents. An analysis of cross-sectional data from three hospital databases (Wolozin et al. 2000) revealed similar findings relating statin use to prevalence of Alzheimer disease. Cross-sectional studies of incident cases from the Canadian Study of Health and Aging (Rockwood et al. 2002) suggested reduced risks of dementia and Alzheimer disease among users of any lipid-lowering agents who were younger than age 80 years. A case-control study in a convenience sample of prevalent cases (Hajjar et al. 2002) reported inverse association of dementia and Alzheimer disease with statin use, as did a cross-sectional popula-

tion-based study of dementia and lipid-lowering agents in general (Rodriguez et al. 2002). Finally, cross-sectional analyses from a randomized trial of estrogen replacement therapies for secondary prevention of cardiovascular outcomes (Yaffe et al. 2002) suggested that women who were also taking statins (but not other lipid-lowering agents) performed better on a cognitive test and were less likely to experience cognitive symptoms. These convergent findings have stimulated interest in the potential of statins for prevention of dementia among the elderly.

Excepting the United Kingdom report, however, none of the previous studies examined the association of statin use with *subsequent* onset of dementia. Three recent prospective studies have examined the association of statin use with dementia, and the results are disappointing. Neither the Cardiovascular Health Study Cognition Study, nor the Cache County Study, nor the Adult Changes in Thought study found any association between prior statin use and subsequent onset of Alzheimer disease or other forms of dementia (Li et al. 2004; Rea et al. 2005; Zandi et al. 2005). In all, these studies examined 8,462 participants with more than 33,000 person-years of experience in which 764 developed Alzheimer disease. In efforts to reconcile these results with the earlier case-control findings, each group of investigators reanalyzed their data using a simulated case-control approach, and each group then found an apparent association between statin use and dementia. A logical explanation of the disparate findings is therefore that elderly people with cognitive disorders are less likely to receive prescriptions for statins (an effect of their cognitive status rather than a cause). The issue is not yet settled, however. Not only do we lack trials data but one of the three longitudinal studies showed some suggestion of protection in younger participants or those with an APOE ε4 allele, reminiscent of the case-control work from the Canadian Study (Li et al. 2004). More recently, Li et al. (2007) demonstrated reduced neurofibrillary change in the autopsied brains of deceased statin users.

There are also laboratory findings to suggest that high cholesterol may influence the pathogenesis of Alzheimer disease directly. Experiments both in vivo (Refolo et al. 2000; Sparks et al. 1994) and in vitro (Fassbender et al. 2001; Frears et al. 1999; Racchi et al. 1997; Simons et al. 1998; Urmoneit et al. 1998) suggest that cholesterol accelerates the production of Aβ by shifting amyloid precursor protein metabolism from alpha to beta cleavage products (see Chapter 24 of this volume, "The Molecular and Genetic Basis of Alzheimer Disease"). Statins may inhibit this process by lowering available cholesterol. Alternatively, statins may prevent atherothrombotic events by action on smooth muscle function, macrophages, and platelets (Hess et al. 2000), or they may reduce inflammatory responses thought to be important in Alzheimer pathogenesis (Akiyama et al. 2000) by inhibiting nitric oxide synthase (Pahan et al. 1997).

There are as yet no published randomized, controlled trials of statins for prevention of dementia, but three randomized trials have examined cognitive decline as a secondary end point, finding no evidence for a protective effect. In 431 subjects age 65 years or older randomized to lovastatin or placebo for 6 months, there were no treatment-related differences in performance over time on cognitive function scales (Santanello et al. 1997). The United Kingdom Heart Protection Study randomized 20,536 high-risk older adults (aged 40–80 years) to simvastatin or placebo for approximately 5 years but found no differences in performance on a telephone assessment of cognition at the participants' final visit (MRC/BHF Heart Protection Study 2002). The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial randomized 5,804 high-risk elderly (age 70–82 years) to pravastatin or placebo for approximately 3 years but found no effect of treatment on cognitive outcomes (Shepherd et al. 2002).

Although some of these findings have dampened enthusiasm to a degree, statins remain a viable candidate for primary prevention trials.

Hormone replacement therapies

A number of case-control observational studies have reported mixed results after examining alteration in the incidence of Alzheimer dementia among women who have taken postmenopausal estrogen replacement therapy (ERT) (Amaducci et al. 1986; Baldereschi et al. 1998; Broe et al. 1990; Graves et al. 1990; Henderson et al. 1994; Heyman et al. 1984; Lerner et al. 1997; Mayeux and Tang 1996; Mortel and Meyer 1995; Paganini-Hill and Henderson 1994). One such study found no relation between Alzheimer incidence and HRT ascertained from pharmacy records, with both incident cases and exposures drawn within a 10-year period (Brenner et al. 1994). Another investigation using pharmacy records—but counting exposures over women's lifetimes—showed an inverse relationship of Alzheimer dementia and ERT use (Waring et al. 1997). Four cohort studies have been published (Kawas et al. 1997; Mayeux and Tang 1996; Seshadri et al. 2001; Zandi et al. 2002b), all but one showing apparent protection with estrogen use (Seshadri et al. 2001). Notably, the latter study again restricted both case detection and exposure measurement to the same 10-year window of observation. Thus, the observational literature suggests that ERT use may protect against onset of Alzheimer disease provided such use predates the onset of dementia by a decade or more (most such use typically being at the years of menopause and the decade or two following.)

An enormous literature suggests neurotrophic or neuroprotective influence of estrogen in neuronal cultures and in vivo (reviewed by Morrison et al. 2006). An interesting finding is a series of cell culture experiments showing that estrogen added to neuronal cultures before exposure to $A\beta_{42}$ protects against apoptotic cell death, whereas addition of estrogen after such exposure accelerates cell death (Chen et al. 2006; Nilsen et al. 2006). Based on the observational evidence and some of the earlier laboratory studies, there was considerable interest in the potential of postmenopausal HRT for protection against Alzheimer disease and other dementias.

As is well known, the trials data have not yielded the desired results. Several treatment trials showed no benefit, and even the possibility of harm, when estrogens were administered to women with symptomatic Alzheimer dementia (Henderson et al. 2000; Mulnard et al. 2000; Resnick et al. 2002). An interesting exception to these findings was the suggestion of improved outcomes when estrogen (specifically the naturally occurring human form, 17-beta estradiol) was administered in pilot studies by transdermal patch (Asthana et al. 2001). Expansion of the latter finding with an adequate sample size was preempted by the discouraging results of the randomized, controlled trial of conjugated estrogen equine (with or without coadministration of progestin) in the Women's Health Initiative. Among other disappointing results, the estrogen-plus-progestin arm of this trial suggested no cognitive benefit overall and an increased risk of dementia among previously healthy women (Rapp et al. 2003; Shumaker et al. 2003); and the estrogen-alone arm showed no benefit and a suggestion of harm (Rapp et al. 2003; Shumaker et al. 2003, 2004).

Although they have been cause for marked retrenchment in human research on estrogens and prevention of dementia, the Women's Health Initiative findings should not be considered the final word on this topic. As noted earlier, a number of investigators and experts have suggested that the issue of timing of administration of estrogens (peri- or early postmenopausal treatments vs. initiation in old age) may be critical, and both laboratory findings (Chen et al. 2006) and observational study results suggest the existence of a dichotomy in effect between treatments in the decade preceding onset of dementia versus earlier use (Breitner and Zandi 2003; Zandi et al. 2002b).

Histamine H_2 blockers

There are only four approved drugs in this histamine blocker class. They are cimetidine, ranitidine, nizatidine, and famotidine. Interest in these drugs for the prevention of Alzheimer disease arose with a study of environmental exposures in disease-discordant or onset-discordant siblings from families with familial late-onset Alzheimer disease (Breitner et al. 1995). In addition to confirming the inverse association of NSAID use and incident Alzheimer disease, the study also found an inverse association of dementia with prior H_2 blocker use. Because this finding had not been hypothesized, and because H_2 blockers are among the safest known medicines, its replication was essential. However, such replication has proven difficult. The Rotterdam Study could not confirm the finding in a cross-sectional analysis of Alzheimer cases ascertained from a large population (Launer et al. 1997), but this study did not examine possible effects of H_2 blocker use *before* Alzheimer disease onset. More importantly, in the early 1990s the prescription use of H_2 blockers was largely supplanted by omeprazole and other proton pump inhibitors. At the same time, the H_2 blockers as a class became available over the counter. The result was that, from the mid-1990s onward, the use of H_2 blockers has typically been sporadic, for temporary relief of symptoms; their regular use for treatment of gastroesophageal reflux disease or peptic ulcer disease has become uncommon.

These events created obstacles for observational studies that would have sought association between regular use of H_2 blockers and Alzheimer disease. Yet such observational studies are needed before anyone can realistically argue for costly randomized prevention trials. We know of two populations that have been monitored regularly for the occurrence of Alzheimer disease and where good pharmacological exposure data are available, from the 1970s in one instance and the beginning of the 1990s in the other. If they can confirm the inverse association of Alzheimer risk with use of H_2 blockers, analyses of these observational data sets (currently under way) will be of considerable interest.

There is very little animal work investigating a possible neuroprotective effect of H_2 blockers, and there is only one trial in humans, which did not suggest any benefit but was markedly underpowered (Carlson et al. 2002).

Conclusion

Because of the enormous public health problem posed by the dementias of aging, the development of successful strategies for their prevention is essential. We have described a series of principles and strategies aimed at the prevention of dementia symptoms in people who appear to have prodromal disease or at primary prevention in those who are asymptomatic. The many disappointments from these efforts should not deter us from further work,

but they may suggest that we have far to go in understanding the etiology and pathogenesis of Alzheimer disease and other dementias of aging. By contrast, the seemingly incongruous results of observational studies and randomized trials should be instructive—either regarding the pitfalls of observational studies or, more probably, regarding the variable effects of several interventions at different stages of disease progression. To a degree not previously realized, early application of many interventions may be essential for beneficial results. Other lessons learned in recent years concern the paramount need for safety of long-term interventions for primary prevention and a more realistic understanding of the costs and difficulties in the conduct of trials for primary prevention of dementia. There are at least three candidate pharmaceutical/neutriceutical strategies (statins, H_2 blockers, and combined fat- and water-soluble antioxidant vitamins) that have not yet been adequately tested but might theoretically be evaluated in trials for primary prevention. Other candidate interventions include mental or physical conditioning, treatments leading to improvements in cardiovascular health, or alterations in nutrition.

In all events, we must persevere. To paraphrase Fredrickson again, seeing what otherwise lies before so many of us, have we really any choice?

KEY POINTS

- From a public health perspective, strategies for prevention of the dementia of Alzheimer disease are preferable to successful treatments.
- The pathogenesis of Alzheimer disease includes a latent stage and, in many instances, a prodrome. The dementia of Alzheimer disease is in fact an end stage of the disease.
- Prevention of advance from the prodrome to the dementia of Alzheimer disease—that is, secondary prevention—is less valuable than primary prevention strategies that are applied in the latent stage to prevent symptoms altogether.
- Identification of the Alzheimer disease prodrome, and its differentiation from other mild cognitive syndromes, will be important advances in the methodology of secondary prevention trials.
- A number of "lifestyle" factors and pharmaceutical exposures have been examined in observational studies, where they have shown promise as primary prevention strategies. A number of these remain to be tested in randomized prevention trials.
- Primary prevention trials require very large sample sizes and extended observations, making them very costly. They are also inherently vulnerable to unexpected safety concerns. But "have we really any choice?"

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Appendixes

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Appendix A

History Form

Patient name _____ Date of birth _____ Education (years) _____

Occupation/Former occupation _____

Person completing this form_____ Relation to patient_____

Please answer the following questions to the best of your ability. If you don't know the answer, just check "Don't know." This questionnaire is long, but it serves several important purposes; it stimulates you to think about your own observations in greater depth and detail and helps you to include information you might not have thought important. And it will be read.

1) Was onset of problem with memory, language, or daily function sudden ___ or gradual ___?

2) Has there been a steady progression ___, abrupt decline ___, or no progression ___?

Is there a problem with:	**Yes**	**No**	**Don't know**	**Date**
MEMORY				
3) Remembering people's names	_____	_____	_____	_____
4) Recognizing familiar faces	_____	_____	_____	_____
5) Finding way indoors	_____	_____	_____	_____
6) Finding way on familiar streets	_____	_____	_____	_____
7) Remembering a short list of items	_____	_____	_____	_____
8) More confusion late in the day	_____	_____	_____	_____
EXPRESSION				
9) Finding the right word	_____	_____	_____	_____
10) Understanding words	_____	_____	_____	_____
DAILY FUNCTIONING				
11) Trouble with household tasks	_____	_____	_____	_____
12) Trouble handling money	_____	_____	_____	_____

	Yes	No	Don't know	Date
13) Doesn't grasp situations or explanations	_____	_____	_____	_____
14) Difficulty at work (check if N/A ____)	_____	_____	_____	_____
15) Trouble dressing or caring for self	_____	_____	_____	_____
16) Trouble feeding self	_____	_____	_____	_____
17) Trouble controlling bladder and bowels	_____	_____	_____	_____
PERSONALITY				
18) More irritable	_____	_____	_____	_____
19) Less interested	_____	_____	_____	_____
20) Less sensitive to others	_____	_____	_____	_____
21) Loss of social graces or manners	_____	_____	_____	_____
22) Loss of initiative	_____	_____	_____	_____
23) Physical violence	_____	_____	_____	_____
24) Developed odd habits or interests	_____	_____	_____	_____
SLEEPING AND EATING				
25) Excessive daytime sleepiness	_____	_____	_____	_____
26) Vivid dreams; dreams seem real	_____	_____	_____	_____
27) Violent movement/talking in sleep	_____	_____	_____	_____
28) Overeating/Consuming sweets	_____	_____	_____	_____
29) Appetite loss	_____	_____	_____	_____
30) Eating nonfood substances	_____	_____	_____	_____
THINKING				
31) More suspicious	_____	_____	_____	_____
32) Delusions or false beliefs	_____	_____	_____	_____
33) Hallucinations (sight, sound, odor)	_____	_____	_____	_____
34) Illusions; mistakes one thing for another	_____	_____	_____	_____
35) Thinks others are doubles or imposters	_____	_____	_____	_____
36) Talks of suicide or attempts suicide	_____	_____	_____	_____
37) Aware of having a problem	_____	_____	_____	_____
OTHER PROBLEMS				
38) Poor hearing	_____	_____	_____	_____
39) Poor eyesight	_____	_____	_____	_____

	Yes	No	Don't know	Date
40) High cholesterol	_____	_____	_____	_____
41) Stroke(s)	_____	_____	_____	_____
42) High blood pressure	_____	_____	_____	_____
43) Heart attack	_____	_____	_____	_____
44) Abnormal heart beat	_____	_____	_____	_____
45) Unexplained falls	_____	_____	_____	_____
46) Parkinson disease (shaking, shuffling gait)	_____	_____	_____	_____
47) Fainting spells	_____	_____	_____	_____
48) Head injury with loss of consciousness	_____	_____	_____	_____
49) Seizure or epilepsy	_____	_____	_____	_____
50) Brain tumor	_____	_____	_____	_____
51) Diabetes	_____	_____	_____	_____
52) High or low thyroid function	_____	_____	_____	_____
53) Treated for mental/emotional problems	_____	_____	_____	_____

a. Diagnosis _____

b. Hospitalized Yes ___ No ___

54) Down syndrome Self ___ Family member ___

55) Other medical problems _____

56) Drugs: medication for memory?	_____	_____	_____	_____

a. _____

b. _____

c. _____

d. _____

57) Drugs: medication for calming?	_____	_____	_____	_____

a. _____

b. _____

c. _____

d. _____

Side effects (specify) _____

58) Illegal street drugs?	_____	_____	_____	_____

a. Other drug abuse/dependence (presecription, etc.)? _____

59) Alcohol use	_____	_____	_____	_____

a. Current number of ounces per week: _____

	Yes	No	Don't know	Date
60) Alcohol abuse	_____	_____	_____	_____
61) Toxic chemical exposure	_____	_____	_____	_____
a. Type _____				
62) Syphilis	_____	_____	_____	_____
63) Other infection (HIV, hepatitis, etc.)	_____	_____	_____	_____
a. Specify _____				
64) Cancer (other than skin)	_____	_____	_____	_____
a. Type _____				
b. Treatment: none ___ radiation ___ chemotherapy ___ surgery ___ other ___ (check all appropriate)				
65) Cataract surgery or other eye surgery	_____	_____	_____	_____
66) Surgery with general anesthesia	_____	_____	_____	_____
a. _____				
b. _____				
c. _____				
d. _____				
67) CAT scan or MRI (head)	_____	_____	_____	_____
68) Allergies	_____	_____	_____	_____
a. Type _____				
69) Anyone in family with similar problem	_____	_____	_____	_____
a. Relationship to patient _____				
70) Ever had psychiatric neurological exam	_____	_____	_____	_____
a. Diagnosis _____				

71) Name and address of doctors seen for same or similar problems

_____

_____

_____

Source. Adapted from Breitner JCS, Folstein MF: "Familial Alzheimer Dementia: A Prevalent Disorder With Specific Features." *Psychological Medicine* 14:63–80, 1984. Used with permission.

Appendix B

Level of Function Scale

Please circle the patient's level of function at these tasks of everyday life.

	Independent, as good as ever	Independent, not as good as past	Needs prompting or reminding to perform task	Needs hands-on help or step-by-step directions	Can't do, depends on others to do
Work responsibilities	0	1	2	3	4
Hobbies	0	1	2	3	4
Household chores	0	1	2	3	4
Shopping for needs	0	1	2	3	4
Driving	0	1	2	3	4
Appointments	0	1	2	3	4
Finding one's things	0	1	2	3	4
Dressing	0	1	2	3	4
Washing/Grooming	0	1	2	3	4
Eating	0	1	2	3	4
Toileting	0	1	2	3	4
Other:	0	1	2	3	4
Other:	0	1	2	3	4
Anything else you'd like to mention?					

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Appendix C

Mental Status Examination

Patient name _____ Date ___/___/___

Handedness ___ R ___ L Age ____ Sex ___ Marital status _____

Years of education _____ Occupation _____

1. APPEARANCE AND BEHAVIOR	Norm	Abn	Unk
Grooming and dress (circle one):	0	1	9
Hearing _____	0	1	9
Eyesight _____	0	1	9
2. BEHAVIORAL HISTORY OR OBSERVATION			
Wandering _____	0	1	9
Verbal aggression _____	0	1	9
Sundowning _____	0	1	9
Physical aggression _____	0	1	9
Apathy _____	0	1	9
Crying _____	0	1	9

3. ORIENTATION

Time ____ day ____ date ____ month ____ year

Place ____ city ____ hospital ____ home address

Person ____ name ____ age ____ birth date

	Norm	Abn	Unk
4. EMOTION (AFFECT)			
Blunted	0	1	9
Shallow	0	1	9
Labile	0	1	9
Appropriateness	0	1	9
Other	0	1	9
5. MOOD			
Depressed	0	1	9
Euphoric	0	1	9
Other	0	1	9
6. THOUGHT PROCESS			
Associations			
Loose	0	1	9
Klang	0	1	9
Other	0	1	9
Flow			
Tangential	0	1	9
Circumstantial	0	1	9
Flight of ideas	0	1	9
Blockage	0	1	9
Derailment	0	1	9
Perseveration	0	1	9
Other	0	1	9
7. THOUGHT CONTENT			
Delusions	0	1	9
Hallucinations	0	1	9
Illusions	0	1	9
Suspicions	0	1	9
Misidentification syndrome	0	1	9

8. ATTENTION		Norm	Abn	Unk
3-7				
2-4-9	Digits forward	0	1	9
8-5-2-7				
2-9-6-8-3	Digits reversed	0	1	9
5-7-1-9-4-6				
8-1-5-9-3-6-2				
3-9-8-2-5-1-4-7				
CONCENTRATION				
Subtraction of 3s (20, 17, 14, 11, 8, 5, 2, –1)		0	1	9

9. LANGUAGE

Articulation _____ 0 1 9

Fluency overall _____ 0 1 9

____ increase ____ decrease ____ delayed word finding

____ neologisms ____ paraphasias

____ other _____

10. Name as many animals as you can in 1 minute 0 1 9

(normal = 18±6)

11. EXPRESSIVE LANGUAGE	None	Mild–mod	Severe	Unk
Word-finding difficulty in spontaneous speech _____	0	1	2	9
Global rating of amount of spoken language _____	0	1	2	9

12. COMPREHENSION	Norm 0	Abn 1	Unk 9

____ Point to floor ____ ceiling ____ desk, chair, door

____ Are you 150 years old? ____ Is the sky green?

____ Do you put on your coat before or after your shirt/blouse?

____ If you cross from the north to the south side of the street,
which side are you on?

____ Is my cousin's mother a man or a woman?

	Norm	Abn	Unk
13. REPETITION	0	1	9
____ walk ____ hospital ____ Mississippi River			
____ the little boy next door			
____ I saw the train arrive yesterday			
14. NAMING	0	1	9
____ watch ____ back ____ crystal ____ band ____ stem			
15. READING ALOUD (see p. 481)			
P G R	0	1	9
I am going to a movie.	0	1	9
It is a thriller and bound to be scary.	0	1	9
16. WRITING (see p. 482)			
Dictated sentence	0	1	9
Spontaneous sentence	0	1	9
17. MEMORY			
Remote: Name four presidents during your lifetime	0	1	9
Recent: **unrelated words** **5 minutes** **cued**			
book _____ _____	0	1	9
chair _____ _____	0	1	9
green _____ _____	0	1	9
18. PRAXIS			
Imitation	0	1	9
Ideomotor:			
Salute flag	0	1	9
Comb hair	0	1	9
Blow out match	0	1	9
Construction (see p. 482)	0	1	9
____ intersecting rectangles	0	1	9
____ Greek cross	0	1	9
____ cube	0	1	9

19. HIGHER COGNITIVE FUNCTION	Norm	Abn	Unk
Fund of information	0	1	9

____ How many weeks in a year?
____ Why do people have lungs?
____ Name four states.
____ Where is Denmark?
____ How far is it from New York to Los Angeles?
____ Who wrote the *Odyssey?*
____ Why are light-colored clothes cooler in the summer than-dark colored clothes?
____ Who was president during the American Civil War?
____ What causes rust?
____ What is the Koran?

20. CALCULATION			
2×2=4, 2×4=8, 2×8=16, … (through 1,024)	0	1	9

21. PROVERBS: What do people mean when they say…

Don't cry over spilled milk.	0	1	9
People who live in glass houses shouldn't throw stones.	0	1	9
Overall rating	0	1	9

22. SIMILARITIES: An apple and a banana are similar in that they are fruits.
What is the similarity between…

potato	—	carrot	_____	0	1	9
cat	—	rabbit	_____	0	1	9
airplane	—	motorcycle	_____	0	1	9
dancing	—	swimming	_____	0	1	9
hot	—	cold	_____	0	1	9
nose	—	tongue	_____	0	1	9
Overall rating				0	1	9

23. JUDGMENT: What would you do if…

You found a sealed, addressed, stamped envelope on the street?	0	1	9
You were in a crowded theater when a fire broke out?	0	1	9
Overall assessment	0	1	9

24. INSIGHT:
0 = normal; total insight into illness and implications
1 = partial awareness of disease or implications
2 = unaware of or denial of symptoms or illness
3 = uncertain or irrelevant response or not applicable

DIAGNOSIS (DSM-IV-TR)

Axis I: Clinical syndromes or conditions that are the focus of treatment:

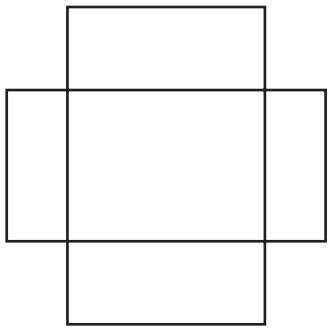
Axis II: Personality or specific developmental disorders:

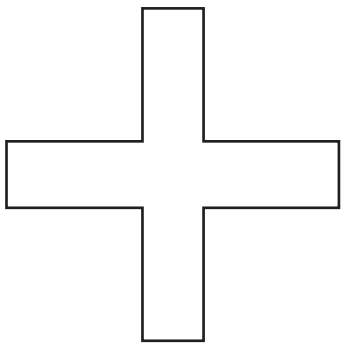
Axis III: Physical disorders and conditions:

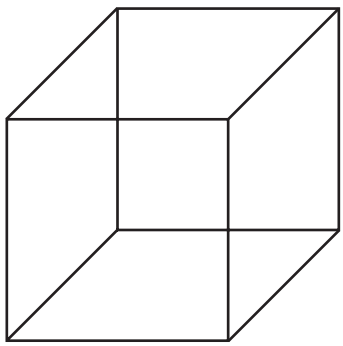
P G R

I AM GOING TO A MOVIE

IT IS A THRILLER AND BOUND TO BE SCARY







Dictated sentence:

Spontaneous sentence:

Draw figures below:

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Appendix D

Neurological Examination

Patient Name: _____

Handedness: R L

Age: _____ Sex: _____ Date: __/__/__

Cranial nerves		**Normal**	**Abnormal**	**N/A**
1.	Olfaction: _____	0	1	9
2.	Visual acuity: _____	0	1	9
3.	Pupils (ERRLA): _____	0	N = neurological P = physical	9
4.	Visual fields: _____	0	1	9
5.	Fund: _____	0	1	9
6.	EOMs: _____	0	1	9
7.	Facial sensation: _____	0	1	9
8.	Muscles of mastication: _____	0	1	9
9.	Jaw jerk: _____	0	1	9
10.	Facial muscles: _____	0	N = neurological P = physical	9
11.	Auditory acuity: _____	0	1 = unilateral 2 = bilateral	9
12.	Palate elevation: _____	0	N = neurological P = physical	9
13.	Cough, gag, swallow: _____	0	1	9
14.	Traps and SCM (CNXI): _____	0	1	9
15.	Tongue: _____	0	1	9

		Normal	Abnormal	N/A
Motor				
16.	Bulk: _____	0	F = focal D = diffuse	9
17.	Spasticity (tone): _____	0	F = focal D = diffuse	9
18.	Fasciculations: _____	0	F = focal D = diffuse	9
19.	Paratonia: _____	0	F = focal D = diffuse	9

20. "Lead pipe" rigidity:	None	Mild	Moderate	Severe	N/A
a) Right extremities:	0	1	2	3	9
b) Left extremities:	0	1	2	3	9

Note: Do not consider cogwheel rigidity here.

21. Strength:

5 = normal	2 = unable to overcome gravity
4 = reduced strength	1 = trace of movement only
3 = unable to overcome	0 = no strength
	9 = N/A

22. Muscle stretch reflexes (circle one for each side)

a) Right		b) Left
1	reflexes reduced but present	1
2	normal	2
3	increased reflexes	3
4	nonsustained clonus	4
5	sustained clonus	5
0	absent reflexes	0
9	N/A	9

		Normal	Abnormal	N/A
23.	Primitive reflexes (check all that apply) ❑ Palmomental ❑ Snout ❑ Grasp ❑ Suck	0	1	9
24.	Extensor plantar response: _____	0	1	9
25.	Finger-nose-finger: _____	0	1	9
26.	Heel-knee-shin: _____	0	1	9
27.	Luria maneuver: _____	0	1	9

		Normal	Abnormal	N/A
28.	Go/no-go:	0	1	9
29.	Motor impersistence: _____	0	1	9
30.	Perseveration: _____	0	1	9
31.	Reciprocal motor command: _____	0	1	9

32. Rapid alternating movements

Right impairment:	None	Mild	Moderate	Severe	N/A
a) Finger or hand clasps	0	1	2	3	9
b) Heel taps	0	1	2	3	9
c) Prone/supine	0	1	2	3	9
Left Impairment:	**None**	**Mild**	**Moderate**	**Severe**	**N/A**
d) Finger or hand clasps	0	1	2	3	9
e) Heel taps	0	1	2	3	9
f) Prone/supine	0	1	2	3	9

33. Abnormal movements		Normal	Abnormal	N/A
a)	Benign essential tremor: _____	0	1	9
b)	Myoclonus: _____	0	1	9
c)	Dyskinesia: _____	0	1	9
d)	Rest tremor–right extremities: _____	0	1	9
e)	Rest tremor–left extremities: _____	0	1	9
f)	Action tremor–right extremities: _____	0	1	9
g)	Action tremor–left extremities: _____	0	1	9

34. Sensation (decreased) (check all that apply)

Normal	Abnormal	N/A
0	F = focal D = diffuse	9

❑ Light touch ❑ Cold
❑ Vibration ❑ Pinprick
❑ Joint position sense

35. Gait and station		Normal	Abnormal	N/A
	Gait and posture: _____	0	1	9
36.	Other extrapyramidal symptoms	0	1	9
a)	Body bradykinesia: _____	0	1	9
b)	Postural stability: _____	0	1	9
c)	Arising from chair: _____	0	1	9
d)	Voice (hypovocalization): _____	0	1	9
e)	Facial movement (hypomimia): _____	0	1	9
f)	Turning en bloc: _____	0	1	9
g)	Cogwheel rigidity: _____	0	1	9

37. Patient cooperativeness (check one)
    - ❑ 0 = fully cooperative
    - ❑ 1 = mildly to moderately cooperative
    - ❑ 2 = very uncooperative
    - ❑ 9 = couldn't examine/don't know

		Normal	Abnormal	N/A
38.	Overall neurological assessment (excluding mental status)	0	1	9
39.	Overall mental status	0	1	9

Notes:

Appendix E

Alzheimer's Disease Cooperative Study: Activities of Daily Living Inventory

The following questions asked of a knowledgeable informant cover the previous 4 weeks:

1. Regarding **eating:** which best describes {S} usual performance during the past 4 weeks?
   - Ate without physical help, and used a knife 3 ❑
   - Used a fork or spoon, but not a knife, to eat 2 ❑
   - Used fingers to eat 1 ❑
   - {S} usually or always was fed by someone else 0 ❑
2. Regarding **walking** (or getting around in a wheelchair), **in the past 4 weeks,** which best describes his/her **optimal** performance?
   - Mobile outside of home without physical help 3 ❑
   - Mobile across a room without physical help 2 ❑
   - Transferred from bed to chair without help 1 ❑
   - Required physical help to walk or transfer 0 ❑
3. Regarding bowel and bladder function **at the toilet**, which best described his/her **usual** performance in the past 4 weeks?
   - Did everything necessary without supervision or help 3 ❑
   - Needed supervision, but no physical help 2 ❑
   - Needed physical help, and was usually continent 1 ❑
   - Needed physical help, and was usually incontinent 0 ❑
4. Regarding **bathing,** in the past 4 weeks, which best describes his/her usual performance?
   - Bathed without reminding or physical help 3 ❑
   - No physical help, but needed supervision/reminders to bathe completely 2 ❑
   - Needed minor physical help, (e.g., with washing hair) to bathe completely 1 ❑
   - Needed to be bathed completely 0 ❑
5. Regarding **grooming**, in the past 4 weeks, which best describes his/her **optimal** performance?
   - Cleaned and cut fingernails without physical help 3 ❑
   - Brushed or combed hair without physical help 2 ❑

Kept face and hands clean without physical help 1 ❑

Needed help for grooming of hair, face, hands, and fingernails 0 ❑

6. Regarding **dressing in the past 4 weeks:**

Did {S} **select** his/her first set of clothes for the day?

Yes ❑

No ❑

Don't know ❑

If yes, which best describes his/her usual performance?

Without supervision or help 3 ❑

With supervision 2 ❑

With physical help 1 ❑

7. Regarding physically getting dressed, which best describes his/her usual performance in the past 4 weeks?

Dressed completely without supervision or physical help 4 ❑

Dressed completely with supervision, but without physical help 3 ❑

Needed physical help only for the buttons, clasps, or shoelaces 2 ❑

Dressed without help if clothes needed no fastening or buttoning 1 ❑

Always needed help, regardless of the type of clothing 0 ❑

8. In the past 4 weeks, did {S} **use a telephone**?

Yes ❑

No ❑

Don't know ❑

If yes, which best describes his/her **highest** level of performance?

Made calls after looking up numbers in white or yellow pages, or by dialing directory assistance 5 ❑

Made calls **only** to well-known numbers, **without** referring to a directory or list 4 ❑

Made calls only to well-known numbers, by using a directory or list 3 ❑

Answered the phone; did not make calls 2 ❑

Did not answer the phone, but spoke when put on the line 1 ❑

9. In the past 4 weeks, did {S} **watch television**?

Yes ❑

No ❑

Don't know ❑

If yes, ask all questions: Did {S}

a – Usually select or ask for different programs or his/her favorite show?

Yes ❑

No ❑

Don't know ❑

b – Usually talk about the content of the program while watching it?

Yes ❑

No ❑

Don't know ❑

c – Talk about the content of the program within a day (24 hours) after watching it?

Yes ❑

No ❑

Don't know ❑

10. In the past 4 weeks, did {S} ever appear to **pay attention to conversation or small talk** for at least 5 minutes? **Note:** {S} did not need to initiate the conversation.

Yes ❑

No ❑

Don't know ❑

If yes, which best describes his/her usual degree of participation?

Usually said things that were related to the topic 3 ❑

Usually said things that were not related to the topic 2 ❑

Rarely or never spoke 1 ❑

11. Did {S} clear the dishes for the table after a meal or snack?

Yes ❑

No ❑

Don't know ❑

If yes, which best describes how he/she usually performed?

Without supervision or help 3 ❑

With supervision 2 ❑

With physical help 1 ❑

12. In the past 4 weeks, did {S} manage to **find his/her personal belongings** at home?

Yes ❑

No ❑

Don't know ❑

If yes, which best describes how he/she usually performed?

Without supervision or help 3 ❑

With supervision 2 ❑

With physical help 1 ❑

13. In the past 4 weeks, did {S} **obtain a hot or cold beverage** for him/herself?

Yes ❑

No ❑

Don't know ❑

If yes, which best describes his/her highest level of performance?

Made a hot beverage, usually without physical help 3 ❑

Made a hot beverage, usually if someone else heated the water 2 ❑

Obtained a cold beverage, usually without physical help 1 ❑

14. In the past 4 weeks, did {S} **make him/herself a meal or snack** at home?

    Yes ❑

    No ❑

    Don't know ❑

    If yes, which best describes his/her highest level of food preparation?

    Cooked or microwaved food, with little or no help 4 ❑

    Cooked or microwaved food, with extensive help 3 ❑

    Mixed or combined food items for a meal or snack, without cooking or microwaving (e.g., made a sandwich) 2 ❑

    Obtained food, on his/her own, without mixing or cooking it 1 ❑

15. In the past 4 weeks, did {S} **dispose of garbage or litter** in an appropriate place or container at home?

    Yes ❑

    No ❑

    Don't know ❑

    If yes, which best describes how he/she usually performed?

    Without supervision or help 3 ❑

    With supervision 2 ❑

    With physical help 1 ❑

16. In the past 4 weeks, did {S} **get around** (or travel) **outside of his/her home**?

    Yes ❑

    No ❑

    Don't know ❑

    If yes, which best describes his/her *optimal* performance?

    Alone, went at least 1 mile away from home 4 ❑

    Alone, but remained within 1 mile away from home 3 ❑

    Only when accompanied with supervised, regardless of the trip 2 ❑

    Only with physical help, regardless of the trip 1 ❑

17. In the past 4 weeks, did {S} ever **go shopping**?

    Yes ❑

    No ❑

    Don't know ❑

    If yes, ask A and B:

    a – Which best describes how {S} usually selects items?

    Without supervision or physical help 3 ❑

    With some supervision or physical help 2 ❑

    Not at all, or selected mainly random or inappropriate items? 1 ❑

    b – Did {S} usually **pay** for items without supervision or physical help?

    Yes ❑

    No ❑

    Don't know ❑

18. In the past 4 weeks, did {S} **keep appointments** or meetings with other people, such as relatives, a doctor, the hairdresser, etc?

    Yes ❑

    No ❑

    Don't know ❑

    If yes, which best describes his/her awareness of the meeting ahead of time?

    Usually remembered, but may have needed written reminders (e.g., notes, a diary, or calendar) 3 ❑

    Only remembered the appointment after verbal reminders on the day 2 ❑

    Usually did not remember, in spite of verbal reminders on the day 1 ❑

    Note: 1. Do not ask Q19 if the {S} is institutionalized; check here:
    2. Being taken to day care or having a sitter at home does not constitute being left alone.

19. In the past 4 weeks, was {S} ever **left on his/her own**?

    Yes ❑

    No ❑

    Don't know ❑

    a – Away from home, 15 minutes or longer, during the day?

    Yes ❑

    No ❑

    Don't know ❑

    b – At home, for an hour or longer, during the day?

    Yes ❑

    No ❑

    Don't know ❑

    c – At home, for less than an hour, during the day?

    Yes ❑

    No ❑

    Don't know ❑

20. In the past 4 weeks, did {S} **talk about current events**? (This means events or incidents that occurred during the past month.)

    Yes ❑

    No ❑

    Don't know ❑

    If yes, ask the following questions: Did {S} talk about events that

    a – He/she heard or read about or saw on TV but did not take part in?

    Yes ❑

    No ❑

    Don't know ❑

b – He/she took part in **outside home** involving family, friends, or neighbors?

Yes ❑

No ❑

Don't know ❑

c – Events that occurred **at home** that he/she took part in or watched?

Yes ❑

No ❑

Don't know ❑

21. In the past 4 weeks, did {S} **read a magazine, newspaper, or book** for more than 5 minutes at a time?

Yes ❑

No ❑

Don't know ❑

If yes, ask the following questions: Did {S} usually

a – Talk about details of what he/she read while, or shortly (< than 1 hour) after, reading?

Yes ❑

No ❑

Don't know ❑

b – Talk about what he/she read 1 hour or longer after reading?

Yes ❑

No ❑

Don't know ❑

22. In the past 4 weeks, did {S} ever write things down?

Note: if {S} wrote things only after encouragement or with help, the response should still be "yes".

Yes ❑

No ❑

Don't know ❑

If yes, which best describes the most complicated things that he/she wrote?

Letters or long notes that other people understood	3 ❑
Short notes or messages that other people understood	2 ❑
His/her signature or name	1 ❑

23. In the past 4 weeks, did {S} perform a **pastime, hobby, or game**?

Yes ❑

No ❑

Don't know ❑

If yes, which pastimes did he/she perform?

Ask about all of the following; check all that apply:

Card or board games (including bridge, chess) ❑

Bingo ❑

Crossword puzzles ❑

Art ❑

Musical Instrument ❑

Knitting ❑

Sewing ❑

Reading ❑

Gardening ❑

Golf ❑

Tennis ❑

Workshop (handicrafts, woodworking) ❑

Fishing ❑

Other, specify_____ ❑

Note: Walking does **NOT** count as a hobby/pastime for this scale.

If {S} performs hobbies/pastimes only at day care, check here. ❑

If yes, how did {S} usually perform his/her most common pastimes?

Without supervision or help 3 ❑

With supervision 2 ❑

With physical help 1 ❑

24. In the past 4 weeks, did {S} **use a household appliance** to do chores?

Yes ❑

No ❑

Don't know ❑

If yes, ask about the following; check all that apply.

Washer ❑

Dryer ❑

Vacuum cleaner ❑

Dishwasher ❑

Toaster ❑

Toaster Oven ❑

Range ❑

Microwave ❑

Food processor ❑

Other, specify_____ ❑

If yes, for **the most commonly used appliances**, which best describes how {S} usually used them?

Without help, operating more than on-off controls if needed 4 ❑

Without help, but operated only on/off controls 3 ❑

With supervision, but no physical help 2 ❑

With physical help 1 ❑

Source. From Galasko D, Bennett D, Sano M, et al: "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." *Alzheimer Disease and Associated Disorders* 11 (Suppl 2):S33–S39, 1997. Used by permission of the NIA Alzheimer's Disease Cooperative Study (NIA AG10483).

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Appendix F

Neuropsychiatric Inventory: Community Dwelling Version

Scoring Sheet

Name (L, F, MI) _____ **Date (M/D/Y)** _____

Item	N/A	Absent	Frequency	Severity	F×S	Disruption
A. Delusions	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
B. Hallucinations	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
C. Agitation	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
D. Depression/dysphoria	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
E. Anxiety	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
F. Euphoria/elation	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
G. Apathy/indifference	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
H. Disinhibition	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
I. Irritability/lability	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
J. Aberrant motor behavior	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
K. Night-time behavior	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5
L. Appetite/eating change	x	0	1 2 3 4	1 2 3	___	0 1 2 3 4 5

1. Informant/Caregiver _____

2. Knowledge of the informant/caregiver about {S}:

   1) very familiar/provides daily care

   2) somewhat familiar/often cares for {S}

   3) not very familiar, has minimal interaction with {S}

3. If caregiver does not live with patient, how many hours per week do they see him/her?

4. Medications of {S} _____

Instructions: Ask the informant/caregiver to indicate whether any of the {S}'s behaviors listed below occurred during the previous four weeks. If so, use the following scales to rate the frequency, severity, and amount of distress the behaviors caused the caregiver.

A. Delusions

Read to the caregiver: *Does {S} have beliefs that you know are not true? For example, insisting that people are trying to harm him/her or steal from him/her. Has he/she said that family members are not who they say they are, or that the house is not their home? I'm not asking about mere suspiciousness: I am interested if {S} is convinced that these things are happening to him/her.*

Yes (If yes, proceed to subquestions 1–10.)

No (If no, proceed to next screening question, "B. Hallucinations.")

N.A. (Not applicable)

_____ 1. Does {S} believe that he/she is in danger—that others are planning to hurt him/her?

_____ 2. Does {S} believe that others are stealing from him/her?

_____ 3. Does {S} believe that his/her spouse is having an affair?

_____ 4. Does {S} believe that unwelcome guests are living in his/her house?

_____ 5. Does {S} believe that his/her spouse or others are not who they claim to be?

_____ 6. Does {S} believe that his/her home is not his/her home?

_____ 7. Does {S} believe that family members plan to abandon him/her?

_____ 8. Does {S} believe that television or magazine figures are actually present in the home/room? [Does he/she try to talk or interact with them?]

_____ 9. Does {S} believe any other unusual things that I haven't asked about?

10. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

10a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—once or more per day.

10b. **Severity** (check one):

1. Mild—delusions present but seem harmless, and do not upset {S} that much.
2. Moderate—delusions are stressful and upsetting to {S} and cause unusual or strange behavior.
3. Marked—delusions are very stressful and upsetting to {S} and cause a major amount of unusual or strange behavior. [PRN medications may be required to control them.]

10c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

B. Hallucinations

Read to the caregiver: *Does {S} have hallucinations such as false visions or voices? Does he/she see, hear, or experience things that are not present?* By this we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if {S} actually has abnormal experiences of sounds, or visions.

Yes (If yes, proceed to subquestions 1–8.)

No (If no proceed to next screening question, "C. Agitation/Aggression.")

N.A. (Not applicable)

_____ 1. Does {S} describe hearing voices or act as if he/she hears voices?

_____ 2. Does {S} talk to people who are not there?

_____ 3. Does {S} describe seeing things not seen by others, or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)?

_____ 4. Does {S} report smelling odors not smelled by others?

_____ 5. Does {S} describe feeling things on his/her skin, or otherwise appear to be feeling things crawling or touching him/her?

_____ 6. Does {S} describe tastes that are without known cause?

_____ 7. Does {S} describe any other unusual sensory experiences?

8. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

8a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—once or more per day.

8b. **Severity** (check one):

1. Mild—hallucinations are present but seem harmless and cause little distress for {S}.
2. Moderate—hallucinations are distressing and are disruptive to {S}.
3. Marked—hallucinations are very disruptive and are a major source of behavioral disturbance. [PRN medications may be required to control them.]

8c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly

3. Moderately
4. Severely
5. Very severely or extremely

C. Agitation/Aggression

Read to the caregiver: *Does {S} have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?*

Yes (If yes, proceed to subquestions 1–9.)

No (If no, proceed to next screening question, "D. Depression/Dysphoria.")

N.A. (Not applicable)

_____ 1. Does {S} get upset when people are trying to care for him/her or resist activities such as bathing or changing clothes?

_____ 2. Is {S} stubborn, having to have things his/her way?

_____ 3. Is {S} uncooperative, resistive to help from others?

_____ 4. Does {S} have any other behaviors that make him/her hard to handle?

_____ 5. Does {S} shout or curse angrily?

_____ 6. Does {S} slam doors, kick furniture, throw things?

_____ 7. Does {S} attempt to hurt or hit others?

_____ 8. Does {S} have any other aggressive or agitated behaviors?

9. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

9a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—once or more per day.

9b. **Severity Ratings** (check one):

1. Mild—behavior is disruptive but can be managed with redirection or reassurance.
2. Moderate—behaviors disruptive and difficult to redirect or control.
3. Marked—agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

9c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

D. Depression/Dysphoria

Read to the caregiver: *Does {S} seem sad or depressed? Does he/she say that he/she feels sad or depressed?*

Yes (If yes, proceed to subquestions 1–9).

No (If no, proceed to next screening question, "E. Anxiety").

N.A. (Not applicable)

_____ 1. Does {S} have periods of tearfulness or sobbing that seem to indicate sadness?

_____ 2. Does {S} say or act as if he/she is sad or in low spirits?

_____ 3. Does {S} put him/herself down or say that he/she feels like a failure?

_____ 4. Does {S} say that he/she is a bad person or deserves to be punished?

_____ 5. Does {S} seem very discouraged or say that he/she has no future?

_____ 6. Does {S} say he/she is a burden to the family or that the family would be better off without him/her?

_____ 7. Does {S} express a wish for death or talk about killing him/herself?

_____ 8. Does {S} show any other signs of depression or sadness?

9. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

9a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—essentially continuously present.

9b. **Severity Ratings** (check one):

1. Mild—depression is distressing, but usually responds to redirection or reassurance.
2. Moderate—depression is distressing, depressive symptoms are spontaneously voiced by {S} and difficult to alleviate.
3. Marked—depression is very distressing and a major source of suffering for {S}.

9c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

E. Anxiety

Read to the caregiver: *Is {S} very nervous, worried, or frightened for no reason? Does he/she seem very tense or fidgety? Is {S} afraid to be apart from you?*

Yes (If yes, proceed to subquestions 1–8.)

No (If no, proceed to next screening question, "F. Elation/Euphoria.")

N.A. (Not applicable)

_____ 1. Does {S} say that he/she is worried about planned events?

_____ 2. Does {S} have periods of feeling shaky, unable to relax, or feeling excessively tense?

_____ 3. Does {S} have periods of or complain of shortness of breath, gasping, or sighing for no reason other than nervousness?

_____ 4. Does {S} complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health.]

_____ 5. Does {S} avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds?

_____ 6. Does {S} become nervous or upset when separated from you [or his/her caregiver]? [Does he/she cling to you to keep from being separated?]

_____ 7. Does {S} show any other signs of anxiety?

8. Have the caregiver rate the frequency, severity, and their own distress for the preceding items.

8a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—once or more per day.

8b. **Severity Ratings** (check one):

1. Mild—anxiety is stressful, but usually responds to redirection or reassurance.
2. Moderate—anxiety is stressful, anxiety symptoms are spontaneously voiced by {S} and difficult to alleviate.
3. Marked—anxiety is very distressing and a major source of suffering.

8c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

F. Elation/Euphoria

Read to the caregiver: *Does {S} seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if {S} has a persistent and abnormally good mood or finds humor where others do not.*

Yes (If yes, proceed to subquestions 1–8.)

No (If no, proceed to next screening question, "G. Apathy/Indifference.")

N.A. (Not applicable)

_____ 1. Does {S} appear to feel too good or to be too happy, different from his/her usual self?

_____ 2. Does {S} find humor and laugh at things that others do not find funny?

_____ 3. Does {S} seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)?

_____ 4. Does {S} tell jokes or make remarks that have little humor?

_____ 5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it?

_____ 6. Does {S} "talk big" or claim to have more abilities or wealth than is true?

_____ 7. Does {S} show any other signs of feeling too good or being too happy?

8. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

8a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—essentially continuously present.

8b. **Severity Ratings** (check one):

1. Mild—{S} is too happy at times.
2. Moderate—{S} is too happy at times, and this sometimes causes strange behavior.
3. Marked—{S} is almost always too happy and finds nearly everything to be funny.

8c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

G. Apathy/Indifference

Read to the caregiver: *Does {S} sit quietly without paying attention to things going on around him/her? Has {S} lost interest in the world around him/her? Has {S} lost interest in doing things or lack motivation for participating in activities? Is it difficult to involve {S} in conversation or in doing chores?*

Yes (If yes, proceed to subquestions 1–9.)

No (If no, proceed to next screening question, "H. Disinhibition.")

N.A. (Not applicable)

_____ 1. Does {S} seem less spontaneous and less active than usual?

_____ 2. Is {S} less likely to initiate a conversation?

_____ 3. Is {S} less affectionate or lacking in emotions when compared to his/her usual self?

_____ 4. Does {S} contribute less to household chores?

_____ 5. Does {S} seem less interested in the activities and plans of others?

_____ 6. Has {S} lost interest in friends and family members?

_____ 7. Is {S} less enthusiastic about his/her usual interests?

_____ 8. Does {S} show any other signs that he/she doesn't care about doing new things?

9. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

9a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—nearly always present.

9b. **Severity Ratings** (check one):

1. Mild—apathy is notable but produces little interference with daily routines; only mildly different from {S}'s usual behavior; {S} responds to suggestions to engage in activities.
2. Moderate—apathy is very evident; may be overcome with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
3. Marked—apathy is very evident and usually fails to respond to any encouragement or external events.

9c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

H. Disinhibition

Read to the caregiver: *Does {S} seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she say things that are embarrassing to you or others?*

Yes (If yes, proceed to subquestions 1–8.)

No (If no, proceed to next screening question, "I. Irritability/Lability.")

N.A. (Not applicable)

_____ 1. Does {S} act impulsively without appearing to consider the consequences?

_____ 2. Does {S} talk to total strangers as if he/she knew them?

_____ 3. Does {S} say things to people that are insensitive or hurt their feelings?

_____ 4. Does {S} say crude things or make sexual remarks that they would not usually have said?

_____ 5. Does {S} talk openly about very personal or private matters not usually discussed in public?

_____ 6. Does {S} take liberties or touch or hug others in a way that is out of character for him/her?

_____ 7. Does {S} show any other signs of loss of control of his/her impulses?

8. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

8a. **Frequency Ratings** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—essentially continuously present.

8b. **Severity Ratings** (check one):

1. Mild—disinhibition is notable, but usually responds to redirection and guidance.
2. Moderate—disinhibition is very evident and difficult to overcome by the caregiver.
3. Marked—disinhibition usually fails to respond to any interventions by the caregiver and is a source of embarrassment or social distress.

8c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

I. Irritability/Lability

Read to the caregiver: *Does {S} get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if {S} has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.*

Yes (If yes, proceed to subquestions 1–8.)

No (If no, proceed to next screening question, "J. Aberrant Motor Behavior.")

N.A. (Not applicable)

_____ 1. Does {S} have a bad temper, "flying off the handle" easily over little things?

_____ 2. Does {S} rapidly change moods from one to another, being fine one minute and angry the next?

_____ 3. Does {S} have sudden flashes of anger?

_____ 4. Is {S} impatient, having trouble coping with delays or waiting for planned activities?

_____ 5. Is {S} cranky and irritable?

_____ 6. Is {S} argumentative and difficult to get along with?

_____ 7. Does {S} show any other signs of irritability?

8. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

8a. **Frequency** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—essentially continuously present.

8b. **Severity** (check one):

1. Mild—irritability or lability is notable but usually responds to redirection and reassurance.
2. Moderate—irritability and lability are very evident and difficult to overcome by the caregiver.
3. Marked—irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

8c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

J. Aberrant Motor Behavior

Read to the caregiver: *Does {S} pace, do things over and over such as opening closets or drawers, or repeatedly pick at things, or wind string or threads?*

Yes (If yes, proceed to subquestions 1–8.)

No (If no, proceed to next screening question, "K. Sleep.")

N.A. (Not applicable)

_____ 1. Does {S} pace around the house without purpose?

_____ 2. Does {S} rummage around opening and unpacking drawers or closets?

_____ 3. Does {S} repeatedly put on and take off clothing?

_____ 4. Does {S} have repetitive activities or "habits" that he/she performs over and over?

_____ 5. Does {S} engage in repetitive activities such as handling buttons, picking, wrapping string, etc.?

_____ 6. Does {S} fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot?

_____ 7. Does {S} do any other activities over and over?

8. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

8a. **Frequency** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—essentially continuously present.

8b. **Severity** (check one):

1. Mild—abnormal motor activity is notable but produces little interference with daily routines.
2. Moderate—abnormal motor activity is very evident; can be overcome by the caregiver.
3. Marked—abnormal motor activity is very evident, it usually fails to respond to any intervention by the caregiver, and is a major source of distress.

8c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

K. Sleep

Read to the caregiver: *Does {S} have difficulty sleeping (do not count as present if {S} simply gets up once or twice per night to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?*

Yes (If yes, proceed to subquestions 1–9.)

No (If no, proceed to next screening question, "L. Appetite and Eating Disorders.")

N.A. (Not applicable)

_____ 1. Does {S} have difficulty falling asleep?

_____ 2. Does {S} get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?

_____ 3. Does {S} wander, pace, or get involved in inappropriate activities at night?

_____ 4. Does {S} awaken you during the night?

_____ 5. Does {S} wake up at night, dress, and plan to go out, thinking that it is morning and time to start the day?

_____ 6. Does {S} wake up too early in the morning (earlier than was his/her habit)?

_____ 7. Does {S} sleep excessively during the day?

_____ 8. Does {S} have any other night-time behaviors that bother you that we haven't talked about?

9. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

9a. **Frequency** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—essentially continuously present.

9b. **Severity** (check one):

1. Mild—night-time behaviors occur but they are not particularly disruptive.
2. Moderate—night-time behaviors occur and disturb {S} and the sleep of the caregiver; more than one type of night-time behavior may be present.
3. Marked—night-time behaviors occur; several types of behavior may be present; {S} is very distressed during the night and the caregiver's sleep is markedly disturbed.

9c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

L. Appetite and Eating Disorders

Read to the caregiver: *Has {S} had any changes in appetite, weight, or eating habits? (Count as NA if {S} is incapacitated and has to be fed.) Has there been any change in type of food he/she prefers?*

Yes (If yes, proceed to subquestions 1–9.)

No

N.A. (Not applicable)

_____ 1. Does {S} have a poor appetite (loss of appetite)?

_____ 2. Does {S} have an abnormally good appetite (increase in appetite)?

_____ 3. Has {S} lost weight?

_____ 4. Has {S} gained weight?

_____ 5. Does {S} have unusual eating behavior, such as putting too much food in his/her mouth at once?

_____ 6. Has {S} had a change in the kind of food he/she likes, such as wanting too many sweets or other specific types of food?

_____ 7. Has {S} developed eating behaviors, such as eating exactly the same types of food each day, or eating the food in exactly the same order?

_____ 8. Have there been any other changes in appetite or eating that I haven't asked about?

9. Have the caregiver rate the global frequency, severity, and their own distress for the preceding items.

9a. **Frequency** (check one):

1. Occasionally—less than once per week.
2. Often—about once per week.
3. Frequently—several times per week, but less than every day.
4. Very frequently—essentially continuously present.

9b. **Severity** (check one):

1. Mild—irritability or lability is notable but usually responds to redirection and reassurance.
2. Moderate—irritability and lability are very evident and difficult to overcome by the caregiver.
3. Marked—irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

9c. **Caregiver Distress** (How emotionally distressing do you find this behavior? Check one):

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

Appendix G

Agitated Behavior in Dementia Scale

Instructions for Administration and Scoring of Agitated Behavior in Dementia Scale (ABID)

The ABID is administered to the caregiver about the Alzheimer's disease patient. Instructions should be read to the caregiver, and the interviewer should ensure that the caregiver understands the instructions.

Each item is rated according to its occurrence during the past week, and according to its occurrence during the week before last, using the following format:

Was (subject) verbally threatening or aggressive towards others during the past week? If yes, mark the frequency, according to instructions. How about the week before last? If yes, mark the frequency. If the behavior occurred during either of the past 2 weeks, ask the caregiver to rate how much the behavior bothered him/her, according to instructions. If the behavior did not occur during either week, mark the reaction as "9" (not applicable).

Continue for each item.

Scoring Algorithm for Outpatient Agitation Inventory:

Reaction total:	sum (r0l to r16)
	range = 0 to 64
	items scored as "9" (not applicable) receive a reaction score of "0"
Frequency total:	first, compute composite score for each item (f01 to f16) by adding
	(week 1 + week 2) for each item
	range for item scores = 0 to 6
	then, sum composite scores (f01 to f16)
	range for total score = 0 to 96

Interview Date: Month_____ Day _____ Year_____

Instructions: The following is a list of problems people/patients sometimes have. Please indicate if any of these problems have occurred during the last two weeks. If so, how much has this bothered or upset you when it happened? Use the following scales for the frequency of the problem and your reaction to it. Please read the description of the ratings carefully.

Frequency Ratings:

0 = did not occur in the week

1 = occurred 1 to 2 times in the week

2 = occurred 3 to 6 times in the week

3 = occurred daily or more often

9 = don't know/not applicable

Reaction Ratings:

0 = not at all

1 = a little

2 = moderately

3 = very much

4 = extremely

9 = don't know/not applicable

Please answer all the questions below. Check one box from 0–9 for both **Frequency** and **Reaction.**

WEEK 1 Refers to the past week

WEEK 2 Refers to the week before last

	Frequency	**Reaction**	
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	1. Verbally threatening or aggressive toward others.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	2. Physically threatening or aggressive toward others.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	3. Harmful to self (e.g., biting, pinching self).
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	4. Inappropriate screaming or crying out.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	5. Destroying property.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	6. Refusing to accept appropriate help (e.g., with personal care).
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	7. Trying to leave (or leaving) home inappropriately.
WEEK 2	❑ ❑ ❑ ❑ ❑		

WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	8. Arguing, irritability, or complaining.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	9. Socially inappropriate behavior (e.g., loud offensive remarks).
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	10. Inappropriate sexual behavior (e.g., unwanted sexual advances, public sexual behavior).
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	11. Restlessness, fidgetiness, inability to sit still.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	12. Worrying, anxiety, and/or fearfulness.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	13. Easily agitated or upset.
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	14. Waking and getting up at night (other than trips to the bathroom).
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	15. Incorrect, distressing beliefs or delusions (e.g., about being threatened or harmed).
WEEK 2	❑ ❑ ❑ ❑ ❑		
WEEK 1	❑ ❑ ❑ ❑ ❑ 0 1 2 3 9	❑ ❑ ❑ ❑ ❑ ❑ 0 1 2 3 4 9	16. Seeing, hearing, or sensing distressing people or things that are not really present (e.g., a strange man in the house, insects crawling on the walls—hallucinations).
WEEK 2	❑ ❑ ❑ ❑ ❑		

Source. Reprinted from Logsdon RG, Teri L, Weiner MF, et al.: "Assessment of Agitation in Alzheimer's Disease: The Agitated Behavior in Dementia Scale: Alzheimer's Disease Cooperative Study." *Journal of the American Geriatrics Society* 47:1354–1358, 1999. Used with permission.

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Appendix H

Quality of Life in Alzheimer's Disease Scale

INSTRUCTIONS FOR INTERVIEWERS

The QOL-AD is administered in interview format to caregivers of individuals with dementia, following the instructions below.

Hand the form to the caregiver, so that he or she may look at it as you give the following instructions (instructions should closely follow the wording given in bold type):

I want to ask you some questions about {S's} quality of life and have you rate different aspects of {S's} life using one of four words: poor, fair, good, or excellent.

Point to each word (poor, fair, good, and excellent) on the form as you say it.

When you think about {S's} life, there are different aspects, like physical health, energy, family, money, and others. I'm going to ask you to rate each of these areas. We want to find out what you think {S} feels about his/her current situation in each area.

If you're not sure about what a question means, you can ask me about it. If you have difficulty rating any item, just give it your best guess.

It is usually apparent whether an individual understands the questions, and most individuals who are able to communicate and respond to simple questions can understand the measure. If the caregiver answers all questions the same, or says something that indicates a lack of understanding, the interviewer is encouraged to clarify the question. However, under no circumstances should the interviewer suggest a specific response. Each of the four possible responses should be presented, and the caregiver should pick one of the four.

If a caregiver is unable to choose a response to a particular item or items, this should be noted in the comments. If the caregiver is unable to comprehend and/or respond to two or more items, the testing may be discontinued and this should be noted in the comments.

As you read the items listed below, ask the caregiver to circle her/his response. If the caregiver has difficulty circling the word, you may ask her/him to point to the word or say the word, and you may circle it for him or her. You should let the participant hold his or her own copy of the measure and follow along as you read each item.

1. *First of all, how do you think {S} feels about {S's} physical health? Would you say it's poor, fair, good, or excellent? Circle whichever word you think best describes {S's} estimate of his/her physical health right now.*
2. *How do you think {S} feels about {S's} energy level? Do you think it is poor, fair, good, or excellent?* [If the participant says that some days are better than others, ask him or her to rate how she/he thinks {S} has been feeling most of the

time lately.]

3. *How would {S} describe {S's} mood lately? Would {S} say {S's} spirits have been good, or would {S} report feeling down? Would {S} rate {S's} mood as poor, fair, good, or excellent?*
4. *How do you think {S} feels about {S's} living situation; the place where {S} lives now? Would you say it's poor, fair, good, or excellent?*
5. *How about {S's} feelings about {S's} memory? Would {S} describe it as poor, fair, good, or excellent?*
6. *How about {S's} family and {S's} relationship with family members? Would you describe it as poor, fair, good, or excellent?* [If the respondent says {S} has no family, ask about brothers, sisters, children, nieces, nephews.]
7. *How do you think {S} would rate {S's} (your) marriage? Do you feel {S} would describe the relationship as poor, fair, good, or excellent?* [Some patients will be accompanied by a nonspousal caregiver. In that case, ask {S's} rating of the relationship with him/her. When this is the case, ask the caregiver how they seem to feel about him/her.]
8. *How would you think {S} would describe {S's} current relationship with friends? Would you say it's poor, fair, good, or excellent?* [If the respondent answers that {S} has no friends, or all their friends have died, probe further. Is there anyone {S} appears to enjoy being with besides family? Would you call that person a friend? If the respondent still says {S} has no friends, ask how does {S} feel about having no friends—poor, fair, good, or excellent?]
9. *How do you think {S} feels about him/herself—when {S} thinks of {S's} whole self, and all the different things about him/her, would you say it's poor, fair, good, or excellent?*
10. *How do you think {S} feels about {S's} ability to do things like chores around the house or other things {S} needs to do? Would you say it's poor, fair, good, or excellent?*
11. *How about {S's} feelings about {S's} ability to do things for fun, that {S} enjoys? Would you say it's poor, fair, good, or excellent?*
12. *How do you think {S} feels about {S's} current situation with money; {S's} financial situation? Would {S} rate it as poor, fair, good, or excellent?* [If the respondent hesitates, explain that you don't want to know what {S's} situation is (as in amount of money), just how they feel about it.]
13. *How do you think {S} would rate {S's} life as a whole; everything together. Would you say it's poor, fair, good, or excellent?*

SCORING INSTRUCTIONS FOR THE QOL

Points are assigned to each item as follows: poor = 1, fair = 2, good = 3, excellent = 4. The total score is the sum of all 13 items.

Patient ID# _____

Patient initials _____

Visit type _____

Date _____

Quality of Life

(Informant Version)

Please rate {S's} current situation, as you see it.

Circle your responses.

1. Physical health.	Poor	Fair	Good	Excellent
2. Energy.	Poor	Fair	Good	Excellent
3. Mood.	Poor	Fair	Good	Excellent
4. Living situation.	Poor	Fair	Good	Excellent
5. Memory.	Poor	Fair	Good	Excellent
6. Family.	Poor	Fair	Good	Excellent
7. Marriage.	Poor	Fair	Good	Excellent
8. Friends.	Poor	Fair	Good	Excellent
9. Self as a whole.	Poor	Fair	Good	Excellent
10. Ability to do chores around the house.	Poor	Fair	Good	Excellent
11. Ability to do things for fun.	Poor	Fair	Good	Excellent
12. Money.	Poor	Fair	Good	Excellent
13. Life as a whole.	Poor	Fair	Good	Excellent

Comments: _____

_____

_____

Thank You!

Patient ID# _____

Patient initials _____

Visit type _____

Date _____

Quality of Life

(Patient Version)

Please rate current situation, as you see it.

Circle your responses.

1. Physical health.	Poor	Fair	Good	Excellent
2. Energy.	Poor	Fair	Good	Excellent
3. Mood.	Poor	Fair	Good	Excellent
4. Living situation.	Poor	Fair	Good	Excellent
5. Memory.	Poor	Fair	Good	Excellent
6. Family.	Poor	Fair	Good	Excellent
7. Marriage.	Poor	Fair	Good	Excellent
8. Friends.	Poor	Fair	Good	Excellent
9. Self as a whole.	Poor	Fair	Good	Excellent
10. Ability to do chores around the house.	Poor	Fair	Good	Excellent
11. Ability to do things for fun.	Poor	Fair	Good	Excellent
12. Money.	Poor	Fair	Good	Excellent
13. Life as a whole.	Poor	Fair	Good	Excellent

Comments: _____

_____

_____

Thank You!

Source. Reprinted from Logsdon RG, Gibbons LE, McCurry SM, et al.: "Quality of Life in Alzheimer's Disease: Patient and Caregiver Reports." *Journal of Mental Health and Aging* 5:21–32, 1999. Copyright 1999, Springer Publishing Company, Inc., New York. Used with permission.

Appendix I

Quality of Life in Late-Stage Dementia (QUALID) Scale

The Quality of Life in Late-Stage Dementia (QUALID) is administered in interview format to an informant following the instructions below.

Informants may be either a family member or professional caregiver who by having regular contact is familiar with the subject's general behavior. Informants must, in addition to being familiar with the subject, have spent a significant portion of at least 3 days out of the last 7 days with the subject, in order to accurately rate the items on the scale. The scale is scored by summing the responses. The possible scores range from 11 to 55, with 11 representing the highest quality of life.

The final items on the scale require that the interviewer make a judgment about the validity of the interview. Provide both a rating of the overall quality of the interview, which includes the informant's ability to understand the items and responses and the effort the informant put forth in answering questions, and the familiarity of the informant with the subject. These items are not included in the score, but offer information about the validity and usefulness of the ratings for that subject.

Informants are handed a blank copy of the scale so that they may look at the items as they are read aloud, and the following instructions are given:

> *I want to ask you some questions about quality of life. I want you to rate his/her behaviors using the responses under each question on this page.* [Point to the responses on the first question.] *There is no one right or wrong answer. I just want to know how you would rate his/her behavior from your observations.*
>
> *Specifically, I want to know about his/her behavior over the past week only, not how he/she previously behaved. Remember that your answers should reflect his/her behavior over the past seven days. If you are not sure what the question means, you can ask me about it. If you have difficulty choosing a rating for an item, just make your best guess. Again, indicate your observation about his/her behavior over the past week.*

Which response best describes _____ over the past week?

A. {S} smiles

1. Spontaneously once or more each day
2. Spontaneously less than once each day
3. Only in response to external stimuli; at least once each day
4. Only in response to external stimuli; less than once each day
5. Rarely, if at all

B. {S} appears sad
   1. Rarely or never
   2. Only in response to external stimuli; less than once each day
   3. Only in response to external stimuli; at least once each day
   4. For no apparent reason less than once each day
   5. For no apparent reason once or more each day

C. {S} cries
   1. Rarely or never
   2. Only in response to external stimuli; less than once each day
   3. Only in response to external stimuli; at least once each day
   4. For no apparent reason less than once each day
   5. For no apparent reason once or more each day

D. {S} has a facial expression of discomfort—appears unhappy or in pain (looks worried, grimaces, furrowed or turned-down brow)
   1. Rarely or never
   2. Less than once each day
   3. At least once each day
   4. Nearly half of each day
   5. Most of each day

E. {S} appears physically uncomfortable—he/she squirms, writhes, frequently changes position
   1. Rarely or never
   2. Less than once each day
   3. At least once each day
   4. Nearly half of each day
   5. Most of each day

F. {S} makes statements or sounds that suggest discontent, unhappiness, or discomfort (complains, groans, screams)
   1. Rarely or never
   2. Only in response to external stimuli; less than once each day
   3. Only in response to external stimuli; at least once each day
   4. Without cause less than once each day
   5. Without cause once or more each day

G. {S} is irritable or aggressive (becomes angry, curses, pushes, or attempts to hurt others)
   1. Rarely or never
   2. Only in response to external stimuli; less than once each day
   3. Only in response to external stimuli; at least once each day
   4. Without cause less than once each day
   5. Without cause once or more each day

H. {S} enjoys eating
   1. At most meals and snacks
   2. Twice a day
   3. At least once a day
   4. Less than once each day
   5. Rarely or never

I. {S} enjoys touching/being touched
   1. Almost always; almost always initiates touching
   2. More than half the time; sometimes initiates touching
   3. Half the time; never initiates touching, but doesn't resist touching
   4. Less than half the time; often or frequently resists touching/being touched
   5. Rarely or never; almost always resists touching/being touched

J. {S} enjoys interacting or being with others
   1. Almost always; almost always initiates interaction with others
   2. More than half the time; sometimes initiates interaction with others
   3. Half the time; never initiates interaction, but doesn't resist interaction with others
   4. Less than half the time; often or frequently resists interacting with others
   5. Rarely or never; almost always resists interacting with others

K. {S} appears emotionally calm and comfortable
   1. Most of each day
   2. More than half of each day
   3. Half of each day
   4. Less than half of each day
   5. Rarely or never

_____ Total Score (sum of all items; scores range from 11 to 55 with lower scores representing higher quality of life)

Quality of Interview (Administrator's judgment):

0 Interview appeared valid

1 Some questions about interview, but probably acceptable

2 Information from interview of doubtful validity

Knowledge/familiarity of caregiver with subject:

0 Very familiar; provides daily care

1 Somewhat familiar; often provides some care

2 Not very familiar; only dispenses meds, minimal contact

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Appendix J

Resources

National Agencies

Administration on Aging
330 Independence Avenue S.W.
Washington, DC 20201
1-800-677-1116
www.aoadhhs.gov/default.html

Alzheimer's Association (National Office)
919 North Michigan Avenue, Suite 1100
Chicago, IL 60611-1676
1-800-272-3900 or 313-335-8700
Fax: 312–335–1110
E-mail: info@alz.org
www.alz.orgA privately funded national voluntary organization with chapters nationwide. The national office can be contacted for information on many issues regarding Alzheimer disease and referral to the nearest local chapter.

Alzheimer's Disease Education and Referral (ADEAR)
P.O. Box 8250
Silver Spring, MD 20907-8250
1-800-438-4380
www.alzheimers.org
This agency is contracted through the National Institute on Aging. ADEAR maintains an online database and functions as a clearinghouse for publications and information on Alzheimer's disease. It has publications from the federally funded Alzheimer's Disease Centers and other sources.

Alzheimer's Foundation of America (AFA)
322 8th Avenue, 7th Floor
New York, NY 10001
1-866-232-8484
www.alzfdn.org
AFA's toll-free hotline provides information, counseling by licensed social workers, and referrals to community resources across the nation.

American Association of Homes and Services for the Aging
2519 Connecticut Avenue, NW
Washington, DC 20008-1520
202-783-2242
www.aahsa.org
Trade association for nonprofit nursing homes, continuing care retirement communities, assisted living, senior housing facilities, and community service organizations offering information for consumers and families.

American Association of Retired Persons (AARP)
Programs Resources Department/BS
601 E Street, NW
Washington, DC 20049
1-800-424-3410
www.aarp.org
AARP distributes resource kits consisting of several publications about aging and caregiving.

The American Parkinson Disease Association, Inc. (APDA)
1250 Hylan Boulevard, Suite 4B
Staten Island, NY 10305-1946
1-800-223-2732, or 718-981-8001
www.apdaparkinson.org
APDA supports research and produces educational materials including a newsletter and various pamphlets covering issues such as nutrition in Parkinson disease and mobility aids.

ARCH National Respite Network and Resource Center
800 Eastowne Drive, Suite 105
Chapel Hill, NC 27514
1-800-473-1727, ext. 222
www.archrespite.org
This national resource center provides resources and information, including a respite locator program, technical assistance to state organizations, and an information clearinghouse.

The Association for Frontotemporal Dementias (AFTD)
100 North 17th Street, Suite 600
Philadelphia, PA 19103
866-507-7222
www.ftd-picks.org/
Genetic, diagnostic testing, caregiving, education, and research information, as well as resources, for patients and caregivers for Pick disease, progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementias.

Children of Aging Parents
1609 Woodbourne Road, Suite 302A
Levittown, PA 19057
1-800-227-7294
www.caps4caregivers.org
This organization provides information, referral services, and educational outreach.

Eldercare Locator
1-800-677-1116
www.eldercare.gov
This nationwide service helps identify local resources for seniors.

Family Caregiver Alliance/National Center on Caregiving
180 Montgomery Street, Suite 1100
San Francisco, CA 94104
800-445-8106
www.caregiver.org
Information on care strategies, stress relief, community resources, family issues, and hands-on care. Also included is a comprehensive collection of family-friendly publications filled with practical information.

Guide to Special Care Units for Alzheimer's and Related Disorders
www.eldercare.com/modules.php?op=modloadandname=CG_Resourcesandfile=articleandsid=885
Provides information and resources for health and well-being, mind and memory, care at home, living alternatives, financial and legal issues, and care for caregivers.

Huntington's Disease Society of America (HDSA)
158 West 29th Street, 7th Floor
New York, NY 10001-5300
800-345-4372 or 212-239-3430
www.hdsa.org
A national voluntary organization providing support and services to patients and families. HDSA also supports research and education and disseminates information. There is also a network of local chapters across the United States.

Lewy Body Dementia Association (LBDA)
P.O. Box 451429
Atlanta, GA 31145-9429
800-539-9767
www.lewybodydementia.org
LBDA assists and informs families, caregivers, and medical professionals. Their outreach services include caregiver help lines (phone and e-mail), a quarterly newsletter, brochures, support groups, and other events.

MedlinePlus
www.nlm.nih.gov/medlineplus/
This is a service of the U.S. National Library of Medicine and the National Institutes of Health that provides information and resources for patients and caregivers with regard to health conditions A to Z and covering a variety of topics within each, such as diagnosis, treatment, rehabilitation, research, and links to other directories and associated organizations.

Assisted living: www.nlm.nih.gov/medlineplus/assistedliving.html

Brain injury: www.nlm.nih.gov/medlineplus/headandbraininjuries.html

Dementia: www.nlm.nih.gov/medlineplus/dementia.html

Stroke: www.nlm.nih.gov/medlineplus/stroke.html

National Association of Professional Geriatric Care Managers
1604 North County Club Road
Tucson, AZ 85716-3101
520-881-8008
www.caremanager.org (maintains national listing)
Case managers are certified to provide an array of assessment and social services ranging from obtaining in-home health help to linking with financial, legal, and other long-term care services.

The National Council on Aging, Inc.
1901 L Street, NW, 4th floor
Washington, DC 20036
202-479-1200
www.ncoa.org/
A private, nonprofit organization that serves as a resource for information, training, technical assistance, advocacy, and leadership in all aspects of aging.

National Head Injury Foundation (NHIF)
1776 Massachusetts Avenue, NW, Suite 100
Washington, DC 20036
1-800-444-6443 or 202-296-6443
www.healthy.net/pan/cso/cioi/NHIF.html
An advocacy organization whose mission is to improve the quality of life for persons with head injures and their families, and to develop programs to prevent head injuries. The NHIF focuses on education, support and information, public awareness, prevention, research, and training.

National Health Information Center
P.O. Box 133
Washington, DC 20013-1133
1-800-336-4797
www.health.gov/nhic
Healthfinder series provides a starting point for consumers and health professionals looking for information on home health care. Currently available books and additional organizations that can provide further information are cited. Financial issues and how to find home health care providers are discussed.

National Institute on Aging (NIA)
Building 31, Room 5C27
31 Center Drive, MSC 2292
Bethesda, MD 20892
301-496-1752
www.nia.nih.gov

National Institute of Neurological Disorder and Stroke (NINDS)
NIH Neurological Institute
P.O. Box 5801
Bethesda, MD 20824
1-800-352-9424
www.ninds.nih.gov/disorders/disorder_index.htm#B

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, MD 20892
301-496-4000
www.nih.gov
National Institutes of Health websites provide information, treatment, prognosis, research, and links to helpful organizations for 27 institutes and centers.

National Organization of Rare Disorders (NORD)
P.O. Box 8923
New Fairfield, CT 06812-8923
1-800-999-6673 or 203-746-6518
www.rarediseases.org
A federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases. NORD is a clearinghouse for information and is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

National Parkinson Foundation (NPF)
1501 Northwest 9th Avenue/Bob Hope Road
Miami, FL 33136-1494
305-243-6666 or 1-800-327-4545
www.parkinson.org
NPF and Bob Hope Parkinson Research Center provide educational services and information in the form of support groups, publications, and workshops. NPF also supports Parkinson disease research.

National Stroke Association (NSA)
9707 East Easter Lane
Englewood, CO 80112
1-800-787-6537
www.stroke.org
A nonprofit organization whose mission is to reduce the incidence and impact of stroke on individuals and on society. It supports stroke research in all areas, develops and distributes educational materials, and is an information and referral clearinghouse.

United Parkinson Foundation (UPF)
833 West Washington Boulevard
Chicago, IL 60607
312-733-1893
www.parkinsons.foundation.org
UPF supports research and provides educational services and information.

Worldwide Education and Awareness for Movement Disorders (WEMOVE)
204 West 84th Street
New York, NY 10024
www.wemove.org
WEMOVE is a not-for-profit organization dedicated to educating and informing patients, professionals and the public about the latest clinical advances, management, and treatment options for neurologic movement disorders.

State Agencies

State Alzheimer Programs
Several states have Alzheimer programs within their state Department of Human Services that provide a variety of services including information and referral. These states include California, Connecticut, Delaware, Florida, Kansas, Massachusetts, Missouri, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Texas, and Wisconsin.

State Department on Aging
See state governmental listing in local telephone directories or see website: www.opm.gov/wrkfam/Elder17.html
These agencies in each state funnel federal dollars to local area Agencies on Aging for disbursement to community agency services and programs for elders. Some programs may be dementia specific. This agency is a good entry point for information and referral for aging services.

State Department of Human Services
www.dhs.state (2 letter state code).us
Provides linkage to state-administered and subsidized programs including community care and adult day care, elder abuse and neglect programs, nursing home and other residential care programs under Title XX.

Nursing Home Ombudsman Programs

Information available regarding quality of care in nursing homes, lists of nursing homes, checklists, etc. Contact the nearest Area Agency on Aging for information on the ombudsman program in your area.

Other Sources of Information

Alzheimer's Forum
www.alzforum.org
A compendium of information for researchers, physicians, and general public, the site includes news, articles, discussion forums, interviews, diagnostic and treatment guide, directory of drugs and clinical trials, and research advances. It also provides access to such unique tools as directory of genetic mutations, antibodies, patents, and conferences.

BenefitsCheckUp
www.benefitscheckup.org
An online service provided by the National Council on Aging. This program allows people to find programs that can help them meet health care costs.

Caregiver's Handbook
www.biostat.wustl.edu/ALZHEIMER/care.html
Provides good coverage on care for the caregiver and is copyright free, making it an excellent training tool.

Caregiver "how to" information
www.webofcare.com
Short animations demonstrate home safety, infection control, personal care, transfers, incontinence care, and more.

Clinical Trials.gov
www.clinicaltrials.gov
Persons with Alzheimer disease, family members, and members of the public can find current trials and research. The searchable database provides information on the name of the study, the purpose, eligibility, and contact information. Additionally, the site indicates whether the study is recruiting and includes citations from published works.

Planning for long-term care
www.alzheimers.org/pubs/longterm.html
This website from the National Institute on Aging explores the options for long-term care, with articles on planning ahead, making the right choice, and making a smooth transition.

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*Page numbers printed in **boldface** type refer to tables or figures.*