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CHAPTER 5

Diagnosis of Alzheimer's Disease

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Impairment of mental function with aging has been alluded to throughout history; however, Alois Alzheimer was the first to describe the clinical course of dementia and associate it with specific pathological changes in the brain (Alzheimer, 1907; see also Jarvik & Greenson, 1987; Katzman, 1996). His case concerned a 55-year-old female whose symptoms began as a paranoid delusion regarding her husband. This initial symptom was followed by memory deterioration and the development of other psychiatric symptoms, including general paranoia and social dysfunction. There was a marked loss of the ability to encode information, with additional neuropsychiatric signs of aphasia, agnosia, and apraxia. Yet her neurologic reflexes were unremarkable. As the disease became more severe, Alzheimer noted bewilderment, psychosis, screaming, and fluctuation of symptoms. After 4.5 years of illness, the patient was bedfast, contracted, and incontinent, and soon died. At autopsy, her brain showed

atrophy, arteriosclerotic changes, neurofibrillary changes, senile plaques, and gliosis. With regard to the clinical presentation with its progressive course and the neuropathology, the description of this patient is typical of the clinical features that are manifested by patients with Alzheimer's disease. Recently, several review articles have discussed the approach to diagnosing this disease, now commonly referred to as dementia of the Alzheimer type (DAT) (Ashford, Schmitt, & Kumar, 1996; Corey-Bloom et al., 1995; Eisdorfer, Sevush, Barry, Kumar, & Loewenstein, 1994; Fleming, Adams, & Petersen, 1995; Geldmacher & Whitehouse, 1996; Katzman & Jackson, 1991; Khachaturian & Radebaugh, 1996; Raskind & Brower, 1996; Siu, 1991).

DAT has features that are common across all patients including an early and insidious development of memory difficulty, which evolves into impairments of language, visual spatial, psychomotor, and executive function (American Psychiatric Association, 1994; McKhann et al., 1984). Diagnostic confirmation requires certain pathological criteria at autopsy, which are consistent with Alzheimer's description of the histopathological changes (Khachaturian, 1985; Mirra & Markesbery, 1996). However, it is now recognized that Alzheimer's disease is a heterogeneous group of disorders (for reviews, see Ashford, Shan, Butler, Rajasekar, & Schmitt, 1995; Boller, Forett, Khachaturian, Poncet, & Christen, 1992; Fisher et al., 1996; Heyman, 1996; Mirra & Markesbery, 1996; Morris, 1996; Roses, 1996). There are variations in this disease's clinical presentation. The initial cognitive impairments are sometimes dominated by language or visual spatial dysfunction (Fisher et al., 1996), or by psychiatric symptoms, including depression and psychosis (Cohen et al., 1993b). Further, the presence of aphasia seems to be associated with an earlier onset and a more rapid disease course (Heyman, 1996; Lawlor, Ryan, Schmeidler, Mohs, & Davis, 1994; Yesavage, Brooks, Taylor, & Tinklenberg, 1993). Also, Parkinsonian or extrapyramidal symptoms are associated with a more rapid progression of the dementia (Chui, Lyness, Sobel, & Schneider, 1994; Mayeux, 1996; Morris, 1996; Stern et al., 1996a), and these symptoms may be associated neuropathologically with the presence of Lewy bodies in the cortex. The concentration of the Alzheimer neuropathological changes in various regions of the brain also can vary in a given patient (Arnold et al., 1991; Arriagada, Growdon, Hedley-White, & Hyman, 1992; Braak & Braak, 1991; Mirra & Markesbery; Ulrich & Stahelin, 1984; Van Hoesen & Solodkin, 1994). For example, the degree to which occipital cortical areas are affected by senile plaques and neurofibrillary tangles

varies considerably from case to case (Lewis, Campbell, Terry, & Morrison, 1987), and visual cortical involvement may be associated with visual spatial deficits (Pietrini et al., 1996) as well as vivid visual hallucinations (Pliskin et al., 1996).

The genetic heterogeneity of DAT is also a well-known disease factor (Roses, 1996). There are at least four chromosomal loci (presenilin-II on chromosome 1; presenilin-I on chromosome 14; apolipoprotein-E on chromosome 19; and the amyloid preprotein on chromosome 21) that contain genetic mutations associated with familial Alzheimer's disease (see chap. 4 of this volume for a discussion of genetic issues in DAT). Specific environmental factors that increase the risk for DAT, such as head injury (Mayeux et al., 1993, 1995; Rasmusson, Brandt, Martin, & Folstein, 1995) and possibly aluminum content in the water supply (Forbes, Gentleman, & Maxwell, 1995), also have been identified, as well as other factors, such as thyroid dysfunction and a history of depressive disorder. Other factors may protect against DAT, such as arthritis or use of anti-inflammatory drugs (Mayeux, 1996). These various factors may result in differences in presentation or onset of DAT symptoms. Nevertheless, there are considerable limitations in the current knowledge base about the precise causes of DAT.

The heterogeneity of DAT leaves diagnosticians with several dilemmas, including early recognition, differential diagnosis, assessment of severity, and distinction of comorbid conditions. As knowledge about DAT grows, clinicians will be able to define particular variants of DAT and how specific factors, including genetic mechanisms, contribute to this syndrome's development and symptom progression. They also will be able to use established clinical criteria to make accurate prognostic statements and therapeutic recommendations.

THE PRECLINICAL AND EARLY PHASE OF DAT

Family members frequently report specific instances that they recollect as marking the beginning of a patient's dementing illness. The initial symptoms frequently relate to an episode of memory dysfunction (Ashford, Kolm, Colliver, Bekian, & Hsu, 1989; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; McCormick et al., 1994; Oppenheim, 1994; Persson & Skoog, 1992; Welsh, Butters, Hughes, Mohs, & Heyman, 1991). However, it is possible that the neural degeneration associated with DAT begins

years, perhaps even decades, before the first symptoms are observed (Katzman, 1993; Ohm, Muller, Braak, & Bohl, 1995; Snowdon et al., 1996). For example, one pathological study examining the deposition of amyloid in the brain suggested that the pathological process may begin early in life (Rumble et al., 1989). Alternatively, high levels of education and initial ability many protect against intellectual decline (Blum & Jarvik, 1974; Stern et al., 1994); however, there are other interpretations, including the possibility that education may mask the early detection of symptoms or lead to a lifestyle associated with less stress or lower likelihood of head trauma or other risk factors (Katzman, 1993, 1996; Mortimer & Graves, 1993). A reasonable speculation is that the hippocampus, which supports new learning and is severely affected in DAT, undergoes a progressive deterioration with age (de Leon et al., 1996; Gallagher et al., 1996), but memory impairments do not occur until fewer than a critical minimal number of neurons remain in the hippocampus (Seab et al., 1988). Further, this threshold of hippocampal neuron loss for emergence of the symptoms of DAT is related to age (Jobst, Hindley, King, & Smith, 1994). However, there is no clear indication of when or how DAT begins or how it progresses to clinical diagnosis.

After the initial cognitive symptom of DAT appears, other cognitive and social dysfunctions develop gradually over a prolonged period of time. During this time period, the emergence of cognitive dysfunction slowly begins to affect the family or those closest to the patient. In most cases, during this early phase of DAT, the persons closest to the patient gradually become concerned, eventually discuss the problem with each other, and finally seek professional advice.

The patient may present the clinician with one or more of many neuropsychiatric symptoms, though the most common difficulty is recent memory dysfunction. Occasionally, DAT patients may present with depression or psychosis, or other predominantly behavioral symptoms. Other neurological symptoms, particularly aphasia, agnosia, apraxia, and disturbance of executive function, frequently occur in DAT patients. In some cases, these symptoms are the presenting features of the disease; however, many of these problems can occur in nondemented elderly individuals with other neurological diseases.

EARLY RECOGNITION OF DAT

An important challenge for clinical medicine is to recognize patients' problems before the crisis that brings them to physicians. Clinicians can

recognize with considerable accuracy in the office cognitive changes associated with dementia using short mental status tests (Meiran, Stuss, Guzman, Lafleche, & Willmer, 1996; Mulligan, Mackinnon, Jorm, Giannakopoulos, & Michel, 1996; Reid et al., 1996; Stuss, Meiran, Guzman, Lafleche, & Willmer, 1996). The most widely used test for screening for early dementia is the Mini-Mental State Exam (MMSE) (Crum, Anthony, Bassett, & Folstein, 1993; Folstein, Folstein, & McHugh, 1975; Tombaugh & McIntyre, 1992). Many studies have examined the performance of elderly individuals on the MMSE and have generally supported the use of a score of 23 or below as a threshold for impaired cognition. However, this test is limited in its ability to distinguish normal individuals from those suffering from mild dementia (Ashford et al., 1989; Fillenbaum, Wilkinson, Welsh, & Mohs, 1994; see chap. 6 of this volume for an additional discussion).

Further, cross-sectional studies have found MMSE scores to decrease with advanced age, and scores also are affected by education (Butler, Ashford, & Snowdon, 1996; Crum et al., 1993; Katzman, 1993, 1996; Teresi et al., 1995). Accordingly, age and education should be used in interpreting a patient's MMSE score (see Table 5.1; Tangalos et al., 1996). However, DAT increases in incidence with age (Katzman, 1996), and DAT may be more prevalent in populations with less education or less occupational attainment (Mortimer & Graves, 1993; Stern et al., 1994).

TABLE 5.1 Mini-Mental State Exam Cutoff Scores for Impaired Cognition and Diagnostic Consideration of Dementia (scores equal to or less than those shown indicate further evaluation)

	Education		
Age	6–11	12–16	16 +
60–69	26	27	29
70–79	24	26	27
80–89	23	24	26
90+	23	23	25

Source: Adapted from "The Mini-Mental State Examination in General Medicine Practice: Clinical Utility and Acceptance," by Tangalos et al., 1996; *Mayo Clinic Proceedings, 71,* pp. 829–837. Copyright 1996 by the *Mayo Clinic Proceedings*. Reprinted with permission; and "Age, Education, and Changes in the Mini-Mental State Exam Scores of Older Women," by Butler et al., 1996, *Journal of the American Geriatrics Society, 44,* pp. 675–681. Copyright 1996 by the *Journal of the American Geriatrics Society*. Reprinted with permission.

Thus an early diagnosis of DAT should take into account the patient's age and education as well as other potentially contributing or confounding conditions (Katzman & Jackson, 1991). Accordingly, DAT diagnosis is generally approached as a dichotomous decision that can be aided by the epidemiologically determined sensitivity and specificity of the cognitive tests using "receiver operating characteristics" (Kukull et al., 1994; Mulligan et al., 1996). However, in early DAT cognitive function diverges from the normal range, not as a dichotomous event, and a patient's status should be calculated on a temporal progression (Ashford et al., 1995), with probability of disease estimated according to the variables that are available (see Table 5.2).

The MMSE is an examination composed of a cross section of items, each with measurable characteristics relevant to the assessment of the DAT patient (Ashford et al., 1989; Fillenbaum, Wilkinson, Welsh, & Mohs, 1994; Teresi et al., 1995), even though these items were not specifically selected for assessing this group of patients. The MMSE can be modified for better utility in the DAT population (Molloy, Alemayehu, & Roberts, 1991), but the original version is so widely used that a change from the present pattern of usage will require the development of a paradigm of major significance. Simple screening questions also may be adapted from the MMSE for telephone screening (Gatz et al., 1995; Lanska, Schmitt, Stewart, & Howe, 1993). However, for initial detection of DAT in the clinician's office, the MMSE may be supplemented with items to strengthen its diagnostic value (Ashford et al., 1992; Cummings & Benson, 1983; Geldmacher & Whitehouse, 1996). For example, the number of animals named in 1 minute is a valuable index for discriminating between DAT patients and normal individuals (Monsch et al., 1994), with most normal individuals able to name at least 15. Also, most normal individuals will know the name of the U.S. president and the immediate past U.S. president, though many mildly demented patients will claim that they do not keep track of such political issues. Abstractions, for example, similarities (oranges and bananas, cats and dogs, tables and chairs), are often difficult for even very mildly impaired patients, but usually present no problem for even very elderly normal people. Modifications of the Boston Naming Test (Knesevich, LaBarge, & Edwards, 1986) can be used to identify the dysnomia associated with DAT. To test visual spatial functions more completely, clock drawing (Watson, Arfken, & Birge, 1993) and drawing a range of objects, such as a circle, a diamond, intersecting rectangles, and a cube, are also useful (Mohs, 1996), though

TABLE 5.2 Dementia Stage Descriptions

Dementia Stage (Type of impairment with clinical findings)	Time-Index (yrs. of disease)	MMSE (range 0–30)	CDRm (range 0–5)	GDS/FAST (range 0–7)
Early Dementia	−2 to 0*	24 to 28	0.5	Stages 2–3
Memory—new learning impaired, slight forgetfulness				
Language—occasional word loss, paraphasia				
Visuospatial—problems with complex designs, unusual objects				
Orientation—difficulty with exact date and time				
ADLs—slight impairment at job, shopping, finances, hobbies				
Psychiatric—depressive symptoms in up to 1/3 of cases				
CT/MRI—minimal cortical atrophy (may not be noted)				
PET/SPECT—mild temporoparietal hypometabolism/hypoperfusion (unilateral or bilateral)				
Mild Dementia	0 to 2.0	19 to 23	1.0	Stage 4
Memory—moderate learning difficulty; defects in remote recall				
Language—reticent, simple conversation, mild anomia				
Visuospatial—mild difficulty identifying, using complex objects				
Orientation—misses date, may become lost in unfamiliar place				
ADLs—less independent function, some prompting in personal care				
Psychiatric—sadness, may have delusions and/or hallucinations				
CT/MRI—mild cortical atrophy, hippocampal thinning apparent				
PET/SPECT—decrease of temporoparietal metabolism/perfusion				
Moderate Dementia	2 to 3.5	11 to 18	2.0	Stage 5
Memory—new information rapidly lost, personal history deficits				
Language—vocabular limitations in conversation, naming deficit				
Visuospatial—difficulty copying simple drawings, using objects				
Orientation—disoriented to time, often to place, becomes lost in less familiar places				
ADLs—no function outside of home, requires assistance with personal care				
Psychiatric—occasional delusions, hallucinations (in 50% of cases with AD)				
CT/MRI—atrophy with ventricular dilatation, large temporal horn				
PET/SPECT—metabolism/perfusion defect begins to affect frontal regions				
Severe Dementia	3.5 to 5	5 to 10	3.0	Stages 6a–6e
Memory—complete loss of recent information, most of remote				
Language—uses simple words, sentences, may name simple objects				

(continued)

TABLE 5.2 *(continued)*

Dementia Stage (Type of impairment with clinical findings)	Time-Index (yrs. of disease)	MMSE (range 0–30)	CDRm (range 0–5)	GDS/FAST (range 0–7)
Visuospatial—severe difficulty using common objects (conceptual & ideational apraxia)				
Orientation—orientation only to person, may not know birth date				
ADLs—no activities, inadequate self-grooming, often incontinent				
Psychiatric—uncooperativity, may get agitated, restless, pace				
CT/MRI—moderate sulcal atrophy, ventricular dilation				
PET/SPECT—patchy loss of temporoparietal & frontal activity				
Profound Dementia	5 to 6.5	0 to 4	4.0	Stages 7a–c
Attention—wandering, patient can be engaged only briefly				
Memory—essentially no memory function, cannot remember family members				
Language—may use single words only, poor comprehension				
Visuospatial—responds meaningfully only to very simple objects				
Orientation—no orientation to self, family members, space, time				
ADLs—full assistance dressing/eating, bowel/bladder incontinent				
Psychiatric—frequent agitation, obliviousness, pacing, or pronounced sleep disturbance				
CT/MRI—severe sulcal atrophy, temporal lobe shriveling				
PET/SPECT—severe loss of temporoparietal & frontal activity				
Complete Dementia	6.5 to 8	0	5.0	Stage 7d–f
Attention—patient is bed/wheelchair bound, no communication				
Language—unintelligible sounds, screaming				
ADLs—unable to ambulate, difficulties with feeding, swallowing				
Psychiatric—screaming, hitting/pinching/biting during ADL care				
Death occurs because of aspiration pneumonia, urinary tract infection, occult severe medical condition: cardiac, ulcer, etc.				

Note. DAT is a progressive disorder not manifesting discrete stages. However, epochs of this illness can be described conveniently using divisions delineated according to severity. The scheme presented in this table was adapted from Reisberg et al., 1994, and Ashford et al., 1995. Time-Index (calculated from data of Ashford et al., 1995); MMSE (Mini-Mental State Exam, Folstein et al., 1975); CDRm (Clinical Dementia Rating Scale, Hughes et al., 1982), modified according to Ashford et al., 1992; GDS/FAST (Global Deterioration Scale/Functional Assessment Staging Measure, Reisberg et al., 1994). Note that the Time-Index is estimated to begin 2 years before diagnosis. Although illness duration is frequently estimated to last 7 to 8 years (see Jost & Grossberg, 1996), the Time-Index carries the assessment to severe levels of dementia that are associated with a high mortality. Reprinted with permission.

the critical issue for mild DAT patients is whether they can draw these shapes from memory.

In an analysis of the items from the "Functional Activities Questionnaire," the question "Do you require assistance remembering appointments, family occasions, or holidays and in taking medications?" was the most accurate screening test (Shankle, Dillencourt, & Pazzani, 1996). With such additions, a clinician can make a fairly comfortable determination that a patient has a clinically significant impairment. Other brief items can be used to enhance further the initial detection of dementia (Mohs, Marin, Green, & Davis, 1996; Welsh et al., 1991). However, all of these tests must be used judiciously and are more meaningful when they are used with respect to values from confirmed normal individuals of similar backgrounds (Sliwinski, Lipton, Buschke, & Stewart, 1996) to determine the point of dysfunction in the time course of the patient's decline (Table 5.2; see also Ashford et al., 1995).

Neuropsychological assessment can often detect early DAT even before family members have recognized symptoms of early DAT or the disease process has significantly impaired day-to-day functions (Schmitt & Sano, 1994). Short cognitive test batteries that focus on associative learning appear to distinguish very mild Alzheimer cases from the normal aging process (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; Welsh et al., 1991) and diagnose DAT with up to 85% accuracy 4 years before it is possible to make a standard clinical diagnosis (Masur et al., 1994; Petersen, et al., 1995). Also, PET brain scanning techniques can identify patients with early DAT with considerable reliability (Kuhl et al., 1987; Small et al., 1989), and further specificity is achieved when apolipoprotein E genotype is considered in relation to the PET scan changes (Reiman et al., 1996; Small et al., 1995; see chap. 7 in this volume for further details). However, at this time, clinicians and health care agencies have not established a practical reason (e.g., preventive interventions or pharmacotherapy) for urging widespread implementation of these early recognition tools.

CLINICAL EXAMINATION OF THE PATIENT WITH DEMENTIA

In the clinical setting, when the patient presents a cognitive problem and a diagnosis of dementia is under consideration, there is a well-accepted diagnostic regimen (see Table 5.3).

TABLE 5.3 Standard Laboratory Tests for Dementia Evaluation

Medical history
Family history
Physical exam
Neurological exam
Mental status exam/neuropsychological assessment
Complete blood count
Estimated sedimentation rate (check for inflammatory processes)
Blood chemistry panel (including liver and kidney function tests)
Serum electrolytes (including magnesium and zinc)
Thyroid function tests
Vitamin B-12/folic acid levels
Serological test for syphilis, HIV
Routine urinalysis
Chest X ray
Electrocardiogram
Brain scan (CT at minimum; MRI and SPECT if available)

Medical History

The first step in the diagnostic regimen is to obtain a complete medical history. Because of the unreliability of the patient's memory, information from a third party is essential. The first issue is to determine the nature of the chief complaint. If memory dysfunction is present, it is critical to determine if this was the first symptom. Memory impairment is a presenting symptom about 50% of the time, but another psychiatric problem such as depression or suspiciousness is present about 30% of the time, while a different cognitive dysfunction or an impairment of day-to-day functions occurs as the symptom that precipitates the initial visit 10% of the time (Oppenheim, 1994).

The next step is to determine whether any specific events or stresses were associated with the occurrence of the first symptom (Guterman et al., 1993). Careful attention must be given to the course of the decline, including an estimation of the accuracy of the retrospective information, to determine if the disease course is progressive or characterized by abrupt changes, such as might be caused by vascular events, metabolic changes, or affective disorders.

A review of the patient's medical history should focus on illnesses that could have caused or contributed to the cognitive impairment. Of particular concern is the use of centrally active medications or toxins. Any medication with anticholinergic side effects could contribute to cognitive dysfunction, including anti-Parkinsonian agents (benztropine, trihexyphenidyl), tricyclic antidepressants (amitriptyline), older antipsychotics (thioridazine), antispasmodics (atropine, scopolamine, l-hyoscyamine, oxybutynin), or antihistamines (diphenhydramine, chlorpheniramine). Several medical conditions, such as head injury and arthritis, and possibly hay fever or asthma and metal work, seem to influence the risk and age at the onset of DAT (Breitner, 1994).

It also is important to obtain a family history of cognitive problems. There has been less interest in recent years in the family history of lymphoma and Down's syndrome although links with DAT have been reported (Heston, Mastri, Anderson, & White, 1981). Although the determination of genetic factors does not have a clear role in the routine diagnostic evaluation, about 40% of patients with Alzheimer's disease have a family history of dementia. The cumulative risk in first-degree relatives of DAT patients is about 50% by 80 years of age, whereas it is about 20% for controls (Breitner, Murphy, Silverman, Mohs, & Davis, 1988). Often, the familial association seems to be related more to longevity than to dementia, but a parent or sibling who had an onset of dementia before 75 years of age strengthens the suspicion of DAT.

Physical Examination

A complete examination is a recommended component of the dementia evaluation. Not only can a variety of systemic conditions, including heart, lung, liver, and kidney disorders contribute to cognitive impairment, but a demented patient may not report medical difficulties adequately. After listening to the heart for murmurs and arrhythmias, the carotids and cranium should be auscultated carefully for bruits. Examination of the retinal fundi can give an estimation of arterial, hypertensive, or diabetic disease, which may suggest a vascular component of the dementia. Retinal photographs can make this exam much easier and more reliable, and contribute more to the diagnosis.

Neurological Examination

While the neurological examination of the DAT patient is usually unremarkable and devoid of focal signs, there are several signs that are typical of DAT patients, and other tests must be performed to rule out important

differential issues (Corey-Bloom et al., 1995; Fleming et al., 1995; Gilman, 1996). A cranial nerve exam should include testing for olfactory function (coffee, cinnamon, etc.). DAT patients are noted for early loss of the ability to identify odors, later losing the capacity to detect smell sensation (Doty, Reyes, & Gregor, 1987; Murphy, Gilmore, Seery, Salmon, & Lasker, 1990; Serby, Larson, & Kalkstein, 1991; Nordin, Monsch, & Murphy, 1995), though many normal adults have difficulty identifying scents as well. The patient's vision (corrected Jaeger reading level) and hearing (tuning fork and rubbing fingers) should be determined because impairment of either visual or auditory function can hamper cognitive performance.

A motor examination usually reveals normal strength and coordination in mild DAT patients, but later there is difficulty following simple commands for testing motor performance along with incoordination. Extrapyramidal motor system signs such as rigidity and tremor can be indications of Parkinson's disease or suggestive of diffuse Lewy body disease, and are associated with a more rapid course of dementia (Chui et al., 1994; Heyman, 1996; Mayeux, 1996; Morris; Stern et al., 1996a). Although DAT patients may not have increased tone, they do have a tendency to not relax, and try to help with passive manipulation, a condition called Gegenhalten. Adventitious movements suggest consideration of Huntington's disease. Gait dysfunction may indicate a variety of problems, but should lead to consideration of normal pressure hydrocephalus, especially with the additional history of bladder control difficulties. Gait problems due to Alzheimer pathology usually develop late in the disease course.

Reflexes in the DAT patient tend to be mildly brisk (Franssen et al., 1991), an indication of cortical dysfunction. Though the snout reflex is frequently present in the normal elderly individual, it is invariably found in the DAT patient and becomes more severe as the disease progresses. Other pathological reflexes are not typically seen in the mild DAT patient and may be more indicative of frontal (palmo-mental, grasp) or Parkinsonian (glabellar) pathology (Galasko, Kwo-on-Yuen, Klauber, & Thal, 1990).

A sensory exam should include testing for vibration. Impairment may indicate a peripheral neuropathy due to vitamin B-12 deficiency or diabetes. The sensory exam is usually intact in the DAT patient, and specific abnormalities should trigger an investigation of the cause.

Focal neurological signs and symptoms should be noted carefully because of their potential relation to stroke and tumor. They are not usually caused by Alzheimer pathology. Particular phenomena that indicate focality are visual field defects, hemiparesis, asymmetric deep tendon reflexes, and an extensor plantar response. Myoclonus and rapid dementia progression suggest Creutzfeldt-Jakob disease.

Neuropsychological Testing

Neuropsychological assessment is an important component of the dementia evaluation. This component of the clinical examination gives the most explicit and objective description of the patient's difficulties and contributes considerably to the differential diagnosis. Neuropsychological measures most directly reflect the loss of brain function caused by Alzheimer pathology. Neuropsychological deficits in DAT reflect the effect of the Alzheimer pathological processes on memory structures and mechanisms. Since DAT primarily involves a loss of memory processing capabilities, other cognitive losses seem to occur in relation to the destruction of memory substrates (see chap. 3 of this volume for a further discussion of this issue). For any measure of DAT to be demonstrated to have reliability, it must correlate with the neuropsychological measures. (For a more extensive discussion of neuropsychological testing, see chap. 6 of this volume.)

Laboratory Tests

A specific list of tests is commonly employed as part of the DAT evaluation (see Table 5.3). However, this regimen should be adjusted for the individual patient (Eisdorfer et al., 1994; Fleming et al., 1995; Siu, 1991).

A cerebrospinal fluid (CSF) examination is usually done only in those cases where cancer or a cerebral infection is considered, particularly syphilis (Corey-Bloom et al., 1995). Several recent studies of CSF have shown that DAT patients have significantly increased levels of the microtubule-associated tau (e.g., Arai et al., 1995) and diminished concentrations of β-amyloid (e.g., Motter et al., 1995). Although these two changes may not constitute a positive diagnosis of DAT, they can give support to consideration of this disease in the differential diagnosis.

Brain Imaging in DAT Diagnosis

Indirect examination of the brain, from pneumoencephalograms and arteriograms of the past to CT/MRI and PET/SPECT scans of the present,

has long been advocated as part of the dementia evaluation. Brain imaging techniques have been improving rapidly for diagnosing Alzheimer's disease. There is general agreement among experts in this field that a brain scan is a justifiable procedure to rule out a tumor, stroke, normal pressure hydrocephalus, or subdural hematoma, in a patient with mild or moderate cognitive dysfunction (Corey-Bloom et al., 1995).

This clinical objective can be accomplished with cerebral tomography (CT) without contrast. However, shrinkage in the medial temporal lobe also can be assessed with this technique to give an accurate estimation of the atrophy associated with Alzheimer's disease (Jobst et al., 1994). The justification for a more extensive or expensive examination such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), or positron emission tomography (PET) is a contested issue. However, techniques for brain imaging and computer analysis are rapidly improving interpretation (Smith, 1996). MRI, particularly of the coronal sections in DAT, shows atrophy of the hippocampus and temporal lobe, which can support the diagnosis of Alzheimer's disease and give an estimation of the severity of the disease process (Jagust, 1994; Jobst et al., 1994), but quantification using this technique is not standardized. PET, measuring metabolic activity, and SPECT, measuring cerebral blood flow, both show characteristic decreases of activity in the temporal and parietal regions of the brain (Herholz, 1995; Schmitt, Shih, & DeKosky, 1992; Small et al., 1989; Stollberger, Fazekas, Payer, & Flooh, 1995; Waldemar et al., 1994).

The combination of morphologic imaging and SPECT can further improve diagnostic power (Jobst et al., 1994; Stollberger et al., 1995), and three-dimensional rendering of PET images also improves DAT diagnosis substantially (Burdette, Minoshima, Borght, Tran, & Kuhl, 1996). PET in conjunction with genotyping also provides better assessment of DAT (Reiman et al., 1996; Small et al., 1995) and may reveal persons who are at risk for DAT. In the future, there will be increased use of the more advanced imaging techniques, especially if radioactive agents to selectively tag neurotransmitter systems or neuropathology are developed, and this approach may lead to definite diagnosis in the living patient. However, the practical utilization of the range of imaging tools available in current clinical practice requires judicious consideration of the diagnostic requirement. (See chap. 7 of this volume for a discussion of the advances in neuroimaging.)

Other approaches to assessing brain function are the electroencephalogram (EEG) and the event-related potential (ERP). The EEG is characteristically slowed in DAT, and this is a reliable, but nonspecific, indicator of cerebral dysfunction, including lateralization. The ERP at a latency of about 300 msec in response to a surprising stimulus (P300) is diminished in amplitude with aging and even more so with dementia, but this change also is considered nonspecific. Topographic mapping can enhance electrophysiological techniques. For example, DAT seems to be associated with a selective loss of P300 energy posteriorly (Ashford et al., 1993), consistent with the posterior temporoparietal dysfunction seen on functional brain scans and the distribution of the pathology at autopsy. With further refinements, these measures may be of more diagnostic utility in the future.

CLINICAL DIAGNOSIS OF DAT

The DSM-IV (American Psychiatric Association, 1994) provides a useful set of criteria to aid in the diagnosis of DAT (see Table 5.4). The central criterion in the clinical diagnosis of DAT is deterioration of memory. However, memory impairment must be accompanied by a disturbance in another higher cognitive function. This disturbance of cognition must represent a decline from a previous higher level of function and interfere

TABLE 5.4 DSM-IV Criteria for Dementia of Alzheimer Type

A. Development of multiple cognitive deficits including both:
   1. memory impairment
   2. one or more additional cognitive disturbances:
      (a) aphasia; (b) apraxia; (c) agnosia; (d) disturbance in executive functioning.
B. These cognitive deficits each cause significant functional impairment and represent a significant decline from a previous level of functioning.
C. Course characterized by gradual onset and continuing decline.
D. The cognitive deficits are not due to:
   1. other central nervous system conditions
   2. systemic conditions
   3. substance-induced conditions.
E. The deficits are not exclusively related to delirium.
F. Another Axis I (psychiatric) disorder does not better account for the disturbance.

Source: Adapted from the American Psychiatric Association, 1994. Copyright 1994 by the American Psychiatric Association. Reprinted with permission.

with social and occupational function. Additionally, the dementia cannot be diagnosed as part of a delirium or another psychiatric disturbance. While these criteria are clinically obvious in moderately to severely demented patients, they may be unclear in patients with very mild DAT or other medical or psychiatric problems (where the diagnosis of DAT is of greatest concern).

Assessment of cognitive dysfunction by the clinician should be based on historical report, direct observation, and objective testing. The memory loss in DAT is specifically a disorder of the ability to encode or learn new information (Ashford et al., 1989; Welsh et al., 1991). As the disease advances, there is a progressive destruction of the fundamental neural substrate of memory, which results in the eventual loss of previously formed memories. As mentioned previously, a structured neuropsychological examination also can give an organized formulation of the cognitive strengths and deficits of the patient, track symptom progression, and aid in early differential diagnosis (Schmitt & Sano, 1994; see also chap. 6 of this volume).

The associated social dysfunction can be estimated effectively through a caregiver report, using the Instrumental and Basic Activities of Daily Living (ADL) scales (Ashford, Kumar, et al., 1992; Galasko, Bennett, & the Alzheimer's Disease Cooperative Study, 1996), the Blessed Dementia Scale (Blessed, Tomlinson, & Roth, 1968), the Alzheimer's Disease Assessment Scale—Noncognitive Battery (Mohs, 1996; Mohs et al., 1996), or other structured interviews. The Blessed Dementia Scale also has been correlated with pathological changes. Some ADL tests are performance based and require the direct observation of patient performance (see chap. 6 of this volume for further discussion of functional assessment). Such tools determine specific skills related to higher level functions such as shopping and management of finances or basic functions such as grooming and toileting. In patients with DAT, scores on cognitive rating scales and ADL scales correspond highly with each other, suggesting that the underlying brain deficit is reflected accurately by both types of measurement (Ashford, Kumar, et al., 1992).

DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Although DAT accounts for at least half of the cases of dementia, the diagnostic criteria for dementia are generic and apply to a syndrome

that can be caused by a multitude of conditions. The routine battery of examinations (Table 5.3) is a practical approach to investigating the possible causes of dementia other than Alzheimer's disease. However, this battery frequently does not clarify the diagnosis because several dementing conditions may coexist (Ashford, Rosenblatt, Bekian, & Hayes, 1987; Chui, Zhang, Victoroff, & Zaias, 1996; Risse et al., 1990; Victoroff, Mack, Lyness, & Chui, 1995). The principal justification for this battery of tests is the search for a reversible or treatable form of dementia (Table 5.5). For example, a frequently discovered problem is the use of centrally active medications whose elimination improves the patient's cognitive function. In the clinical setting, there is a major urgency to discover potentially reversible causes of dementia, because such conditions will become progressively more difficult to arrest or reverse (Eisdorfer et al., 1994). Of most concern are the diagnoses of subdural hematoma, normal pressure hydrocephalus, hypothyroidism, and B-12 deficiency.

An important clinical feature of DAT is the slow and insidious development of the symptoms, while head trauma, surgery, stroke, or a specific hypoxic or hypoglycemic episode can result in a rapid onset of symptoms. Creutzfeldt-Jakob disease, brain tumor, and depression have gradual onset, but usually progress at faster rates than DAT. However, the naturally slow development of other insidious diseases (e.g., thyroid disorder, normal pressure hydrocephalus) may mimic the onset and course of DAT. Further, a series of small strokes without focal neurological findings might induce a progressive loss of cognitive function that is difficult to distinguish from the DAT symptom constellation even with neuropsychological testing and

TABLE 5.5 Reversible and Treatable Dementias

Types
Depression
B-12/folate deficiency
Tumor (especially meningioma)
Subdural hematoma
Normal pressure hydrocephalus
Infections
Toxins
Endocrinopathy

neuroimaging. Consequently, there are no definite clinical features of DAT that can confirm the diagnosis of Alzheimer's disease. For the benefit of the family, a clear diagnosis of dementia should be emphasized, while maintaining the consistent position that a definite diagnosis at this time requires autopsy confirmation; but the possibility or probability of Alzheimer's disease can be estimated clinically based on the typicality of the presentation and the lack of other possible causes of dementia (McKhann et al., 1984). Using this clinical standard, diagnostic accuracy established at autopsy ranges from 60% for "possible" cases to 90% for "probable" cases (Galasko et al., 1994).

As mentioned previously, an important diagnostic and management consideration is the co-occurrence of different types of medical problems in the elderly individual that could account for symptoms of dementia (Ashford et al., 1987; Eisdorfer et al., 1994; Katzman & Jackson, 1991; Risse et al., 1990). Although DAT accounts for more than half of the cases of dementia at autopsy, there are a host of other common conditions that occur in dementia patients, including pulmonary disease, a history of falls and of surgery, any of which also could account for all or even part of the patient's cognitive dysfunction. A history of head injury occurs five times more frequently in DAT patients than the general population, leading to the speculation that certain injuries or stresses may initiate the Alzheimer process, especially when they occur in elderly individuals. Multi-infarct disease, alcoholism, diffuse Lewy-body disease (Weiner et al., 1996), and Parkinson's disease (Aarsland, Tandberg, Larsen, & Cummings, 1996b) also are commonly associated with dementia (Mirra & Markesbery, 1996; Morris, 1996; Victoroff et al., 1995), and the prevalence of these conditions seems to vary according to location (or at least to the institutions conducting the studies).

Argyrophilic grain disease, Pick's disease, and other frontotemporal dementias can be distinguished from DAT due to the initial personality changes and disinhibitions (Mendez, Selwood, Mastri, & Frey, 1993), but these distinctions are not reliable. Other important conditions to consider are Huntington's disease, HIV infection, and Creutzfeldt-Jakob disease. However, existence of these other conditions does not rule out the independent co-occurrence of Alzheimer's disease in a particular patient.

There are other factors that commonly complicate the diagnosis of Alzheimer's disease, such as the history of alcohol abuse. As discussed previously, dementia in the presence of the triad of incontinence, gait disturbance, and memory impairment, accompanied by a characteristic

enlargement of the ventricles seen on brain scans, suggests normal pressure hydrocephalus, which should be excluded by cisternography. Improvement after shunting can be demonstrated by SPECT scanning (Shih & Tasdemiroglu, 1995; Wong, Luciano, MacIntyre, Brunken, Hahn, & Go, 1997).

IMPORTANCE OF VASCULAR CHANGES

The distinction of dementia due to vascular disease is the issue that most complicates the diagnosis of DAT (Katzman & Jackson, 1991). This differentiation has represented a broad focus of study and has served as the primary issue in the study of the diagnostic accuracy of DAT. This issue is critical because there are about 500,000 cases of stroke each year, 150,000 of these being fatal (Bronner, Kanter, & Manson, 1995), whereas there are about 500,000 new cases of DAT each year, with about 500,000 patients dying with DAT. Recently, specific criteria have been proposed for identifying vascular dementias (American Psychiatric Association, 1994; Chui et al., 1992; Roman et al., 1993). However, these diagnostic approaches provide no specific criteria to determine relative combinations of these two common entities. Arteriosclerotic pathology was even described in the first case reported by Alzheimer. Punctate white matter changes on MRI scans, suggestive of pathology in small penetrating arteries, are seen frequently in demented patients, even when the onset and progression have been reported as slow and progressive (Skoog, Palmertz, & Andreasson, 1994). White matter changes are associated with increasing age, hypertension, heart disease, and diabetes (Kent, Haynor, Longstreth, & Larson, 1994), but not with an Alzheimer diagnosis (Erkinjuntti et al., 1994). At the present time, the clinical significance of these white matter changes remains unclear.

An important consideration about vascular dementia is that there are many mechanisms through which vascular abnormalities can impair brain function (Chui et al., 1992; Roman et al., 1993). Blood flow to the brain is exquisitely regulated according to cortical activation (Parks et al., 1989), independently of blood pressure. "Hardening of the arteries" of the brain, alone, though common, is not likely to impair cognition as dramatically as DAT. The most direct concern is embolism, which may originate in the heart or in an atheromata or other lesion of the aorta, the carotid arteries, the circle of Willis, the cerebral arteries, or the small penetrating

arteries directly supplying the cortex or white matter. Large emboli can cause massive strokes, whereas small emboli may cause small lesions, though the extent of cell death in tissue that has suffered ischemia also may vary. Of concern in the differential diagnosis of DAT is that small vessels branch off the middle cerebral artery close to its exit from the circle of Willis and travel long distances to supply the hippocampus, the basal ganglia, and deep white matter. Small lesions associated with emboli or atheromata in these vessels may damage the same region of the brain most affected by DAT, the hippocampus, as well as causing primary loss of long cortico-cortical white matter tracts. Also, strokes affecting specific cortical regions may produce a constellation of impairments that are difficult to distinguish from DAT, such as "angular gyrus syndrome" (Benson, Cummings, & Tsai, 1982). Further, many small strokes could produce a clinical picture indistinguishable from DAT. However, it is no longer considered likely that cognitive impairment requires a nonspecific loss of a definite quantity of brain tissue, such as 100 ml. Also, any nonspecific assortment of large and small strokes is unlikely to present a clinical picture highly similar to DAT. Differences between DAT and vascular dementia are even reported for MMSE performances (Magni et al., 1996).

The Hachinsky Scale was developed to determine the presence of embolic dementia (Hachinski et al., 1975). This scale was modified according to pathological outcome criteria (Rosen, Terry, Fuld, Katzman, & Peck, 1980). Although this scale can help to clarify the diagnosis, a high score does not mean the patient does not have Alzheimer's disease, and a low score may be found in some stroke patients.

Other vascular diatheses must be considered such as hypoperfusion, especially after cardiac or pulmonary arrest or severe hypotension, particularly in "watershed regions" of the cortex that may have naturally poor perfusion. Also, hemorrhagic lesions may cause a variety of symptoms, though they are usually severe and fatal. Hypoperfusion also may be caused by gradual thickening of cerebral artery walls. Any of these processes that leads to brain tissue damage can cause some cognitive impairment. Thus it is often a challenge to separate the clinical presentation of a vascular dementia from the slow, selective decline of memory and other cognitive functions seen in DAT.

There is uncertainty about whether Alzheimer's disease may produce amyloid, which can infiltrate blood vessels and cause vascular insults, or if vascular insults may stress the brain and initiate the Alzheimer pathological process. Microangiopathy is a vascular condition caused by β-amyloid associated with DAT, and can lead to local ischemia, stressing cells and potentially aggravating the DAT process. Also, coronary artery disease seems to be associated with senile plaque formation in the brain (Sparks et al., 1990), and individuals with hypertension have an increased density of neurofibrillary tangles in the brain (Sparks et al., 1995). Consequently, the distinction of vascular dementia and DAT is complicated by primary and mutual causality issues.

In any case, if vascular dementia is suspected, an evaluation, including complete cardiac, aortic, and carotid studies, should be initiated, and all possible efforts should be made to prevent further vascular injury to the brain. Factors associated with stroke should be addressed, including reduction of blood pressure below 135/85, elimination of tobacco exposure and alcohol use, rigorous control of diabetes, obesity, and serum cholesterol, management of diet, supplementation of antioxidants, and appropriate anticoagulation (Bronner et al., 1995). Atrial fibrillation should be treated with warfarin as soon as possible. Notably, cognition may improve after vascular risk factors are controlled (Meyer, Judd, Tawaklna, Rogers, & Mortel, 1986). The appropriate message for the patient and family is that following the recommendations for "stroke-risk reduction" reduces the risk of stroke (Bronner et al., 1995), and there may be some benefit for slowing the Alzheimer process as well.

ASSESSMENT OF DAT SEVERITY AND CLINICAL COURSE

An important component of dementia diagnosis is the assessment of severity. Clinicians have developed a wide range of tools to quantitate dementia severity. The Blessed Dementia Scale (Blessed et al., 1968) was long considered the most reliable because it had been associated with neuropathological changes. Other measures of dementia severity have been developed and studied extensively, such as the Global Deterioration Scale (Reisberg, Sclan, Franssen, Kluger, & Ferris, 1994), the Clinical Dementia Rating Scale (Hughes, Berg, Danziger, Coben, & Martin, 1982), and systematic composites of other scales, which improve precision and reliability of the severity estimate (Ashford, Kumar, et al., 1992).

During the late course of DAT, patients lose so much memory and other cognitive functions that they are no longer able to complete such

tests as the MMSE (Ashford et al., 1989; Auer, Sclan, Yaffee, & Reisberg, 1994). Consequently, approaches have been developed to test patients using observations of basic functions (Haycox, 1984; Reisberg et al., 1994; Teresi, Lawton, Ory, & Holmes, 1994; Volicer, Hurley, Lathi, & Kowall, 1994). At the extreme, the Glasgow Coma Scale assesses rudimentary neurologic functions (Benesch, McDaniel, Cox, & Hamill, 1993) and has been applied to assess end-stage DAT. There also have been analyses of patients based on a regression of function through Piagetian developmental stages (Auer et al., 1994; Cole & Dastoor, 1987; Ronnberg & Ericsson, 1994). Other objective tests relying, in part, on nonverbal responses, such as the Severe Impairment Battery (SIB) (Saxton, McGoingle-Gibson, Swihart, Miller, & Boller, 1990) appear to be reliable and useful for assessing moderate and severe patients with greater dynamic range than the MMSE (Schmitt et al., 1996).

Major problems have resulted from the diversity of assessment tools. Use of different tools leads to poor comparability between studies. Consequently, there is also lack of consensus regarding progression rates and patterns. This lack of coordination has led to failure to develop a system for progressively improving assessment techniques. It has been proposed that all dementia measurement scales can be translated into a "Time-Index," and then be compared directly and meaningfully (Ashford et al., 1995).

An important debate in the assessment of DAT is the issue of heterogeneity, whether subgroups may be identified with significantly separate characteristics or different patterns of symptom development (Eisdorfer et al., 1994; Fisher et al., 1996). Clearly, there is variability in the initial onset and course of DAT which is related to many factors such as age, education, genetic typology, medical and neurologic problems, and other stresses (Guterman et al., 1993). However, the reason for analyzing these factors is to account for a continually greater proportion of the extraneous variables so that the core disease process can be observed more closely. Accounting for more variables allows the clinician and researcher to approach the essential issue of DAT, which is the underlying cause of the dementia (Mayeux, 1996). One model proposes that several factors may contribute to the initiation of the Alzheimer process (e.g., age, head trauma, hypoxia, or a multivalent cation toxicity or imbalance); then normal genetic variations, as well as mutations that interfere with the processing of certain proteins, induce progression down a vulnerable final common pathway, which is thought to involve neuroplastic mechanisms

in the brain (see chap. 3 of this volume). The attack on neuroplastic mechanisms in DAT, presumably involving the processing of the microtubule-associated protein tau and the amyloid precursor protein, may vary topographically from patient to patient. In some instances, one hemisphere or brain region may be affected more severely or rapidly than the other (Fisher et al., 1996; Haxby et al., 1988). This loss of correspondence between the rates of deterioration in the hemispheres could be related to loss of communication through the corpus callosum, which shrinks during DAT progression (Biegon et al., 1994; Janowsky, Kaye, & Carper, 1996). Also, certain pathological processes, such as Lewy bodies, may only affect some patients, contributing further to heterogeneity of the clinical picture (Mirra & Markesbery, 1996; Victoroff et al., 1995; Weiner et al., 1996). However, this complexity of the DAT picture indicates the need to analyze individual clinical characteristics for their relationship to the long-term disease course (Ashford et al., 1989, 1995; Stern et al., 1996b), as well as their capacity to discriminate among diverse clinical entities and biological factors contributing to the progress of the disease.

The principal reason for the failure to develop a uniform tool for quantification of dementia severity is the lack of a fundamental physical standard against which to calibrate assessment scales. However, severity measurement can be translated into an absolute physical quantity, time course (Ashford et al., 1995; Reisberg et al., 1994; Stern et al., 1996b). The average time course across many DAT patients can be used to estimate the duration of the illness and predict the future pattern of the patient's deterioration. Patients with DAT usually follow a typical downhill course that lasts about 10 years, on average, from the first symptoms until the most profound level of impairment, clearly a devastating decline relative to normal aging (Jost & Grossberg, 1996). The two-standard deviation limits of the rate of deterioration suggest that 95% of patients will deteriorate between 0.5 and 1.5 times this rate, or follow a course lasting between 5 and 15 years. This time-course estimation provides the caregivers with a time line of expected changes and, thus, can help the family to prepare for the future (Table 5.2). Further, this approach could be useful in the evaluation of compounds targeted as treatments for DAT.

PSYCHIATRIC MENTAL STATUS EXAMINATION

The evaluation of the psychiatric mental status is an important part of the dementia evaluation, though its importance and implications are over-

looked frequently. Not only may the psychiatric symptoms be associated with the initiation of DAT or a more rapid progression (Chui et al., 1994), but these symptoms are frequently the most distressing to the family and caregivers and are the most amenable to treatment. The psychiatric symptoms that occur most frequently in the DAT patient are agitation, depression, apathy, disorders of behavior, sleep disorders, and psychosis, including paranoia, hallucinations, and delusions (see Table 5.6; Cohen et al., 1993b; Cohen-Mansfield, 1996; Eisdorfer et al., 1994). These symptoms occur as the initial observation in one third of the patients (Oppenheim, 1994), including both depression (Jost & Grossberg, 1996) and psychosis (Pliskin et al., 1996; Rubin & Kinscherf, 1989). In Alzheimer's case, the initial symptom was a paranoid delusion. During the course of the disease, many different psychiatric symptoms can occur, with the frequency of occurrence of different symptoms varying according to the severity of the dementia (Cohen-Mansfield, 1996; Kurita, Blass, Nolan, Black, & Thaler, 1993; Reisberg, Frannssen, Sclan, Kluger, & Ferris, 1989).

Significant depression is commonly reported in DAT, occurring in 25%–30% of the patients (Cohen et al., 1993b; Reifler et al., 1989; Wragg & Jeste, 1989), though major affective disorder is much less common (Bungener, Jouvent, & Derouesne, 1996; Weiner, Edland, & Luszczynska, 1994) and depressive symptomatology is much more common (Cohen et al., 1993b; Teri, 1996). As the dementia becomes more severe, the mood is characterized more by apathy (Devanand et al., 1991), which is associated with frontal and anterior temporal lobe dysfunction (Craig et al., 1996). When evaluating depression, it is important to obtain information from interviews of the patient and a caregiver (Logsdon & Teri, 1995). The Geriatric Depression Scale (Montorio & Izal, 1996), the Hamilton Depression Scale (Hamilton, 1967), or the Cornell Scale for Depression in Dementia (Alexopoulos, Abrams, & Young, 1988) are useful guides for querying the patient and the caregiver about depressive symptoms. Depression is important because depression might be a causative or risk factor in dementia (this is a high stress cerebral state), and the treatment of depression will produce modest improvement of cognitive function in the demented patient (Reifler et al., 1989).

In DAT, agitation is a common problem that defines a wide range of inappropriate behaviors, including aggression, purposeless activity, and verbal disruptiveness (Cohen-Mansfield, 1996; Table 5.6). Agitation is associated with paranoia in men, but with other psychiatric problems in

TABLE 5.6 Domains of Aberrant Behavior in DAT

Mood Disorder
Inactivity, apathy, indifference, lack of initiative
Depressed mood
Excess bodily concern, complaining
Moaning, crying, tearfulness
Manic, elevated mood
Irritable, anxious, nervous
Psychotic Disorder
Distrustful, avoidant
Paranoid delusions, suspicious
Responding to hallucinations
Inappropriate Behavior
Stealing, destroying property
Spitting, inappropriate voiding
Inappropriate robing, disrobing
Verbal sexual advances, physical sexual advances
Aggression, Nonphysical, Verbal
Uncooperative, argumentative
Cursing, angry statements
Demanding, verbal threats
Aggression, Physical
Grabbing, pushing, shoving, hitting, slapping, kicking, scratching, pinching, biting
Throwing things, using weapons, combative, assaultive
Purposeless Motor Activity
Hand-wringing, picking, fidgeting, overactive, rocking
Restless, pacing, aimless wandering
Purposeless Verbal Activity
Repetitive questions
Repetitive speech, sounds
Yelling, screeching, screaming
Moaning, crying, tearfulness
Sleep Disorder
Excess daytime napping
Excess nighttime wandering

(continued)

TABLE 5.6 *(continued)*

Shortened circadian rhythm
Prolonged circadian rhythm
Mealtime Behaviors
Refuses to eat
Throws food, steals food
Hordes, hides food, overeats, binges

Source: Partly adapted from Cohen et al., 1993; Cohen-Mansfield, 1996.

women and is more common in women (Cohen et al., 1993a). Aggressive behaviors are more common in male patients (Cohen-Mansfield) and are associated with psychosis (Aarsland et al., 1996a) and underlying medical illness (Malone, Thompson, & Goodwin, 1993), as well as caregiver depression and having an adult child caregiver without a spouse present (Paveza et al., 1992).

Numerous psychotic symptoms occur in DAT patients, but frequent presentations are paranoid delusions and complex visual hallucinations (Pliskin et al., 1996). Psychotic symptoms are associated with more rapid deterioration (Drevets & Rubin, 1989; Chui et al., 1994), but are frequently responsive to therapeutic interventions (Teri, 1996). Preliminary indications suggest that the new antipsychotic medications, such as risperidone and olanzapine, may be more effective in DAT patients while causing fewer extrapyramidal side effects, when they are used for carefully defined psychotic symptoms. The recognition and treatment of agitation and psychosis is important because these symptoms are upsetting and disruptive to the caregivers and a major precipitant of placement in a long-term care setting. In long-term care settings, agitation places heavy demands on staff time, and aggressive behaviors frequently lead to injuries of staff and other patients.

A particularly common and troublesome problem in DAT patients is disruption of the circadian rhythm (Crosby, Wyles, Verran, & Tynan, 1993), which results in excessive daytime sleeping, nocturnal wandering, and cycles that exceed 24 hours, some as long as 72 hours. Nocturnal disruptiveness is particularly difficult for caregivers, and such behavior may be tolerated poorly in a nursing home if the patient is noisy or enters other patients' rooms. However, this symptom is among the most amenable to pharmacotherapy (Ashford & Zec, 1993). The use of melatonin may even be able to keep the patient's cycle in synchrony with the environment (Brezinski, 1997).

In the DAT patient, especially those that are severely impaired or noncommunicative, assessment of mood, psychotic symptoms, and other bodily discomforts is a very difficult task. However, great strides have been made in the field as numerous behavior assessment tools have been developed (Aarsland et al., 1996a; Cummings et al., 1994; Drachman, Swearer, O'Donnell, Mitchell, & Maloon, 1992; Mack & Patterson, 1994; Mungas, Weiler, Franzi, & Henry, 1989; Patterson & Bolger, 1994; Reisberg et al., 1987; Seltzer & Buswell, 1994; Sinha et al., 1992; Sultzer et al., 1994; Tariot et al., 1995; Teri et al., 1992). These instruments establish several different approaches for assessing the array of aberrant behaviors in DAT patients, using frequency of occurrence, severity, and hierarchical scaling (Table 5.2). These instruments need further refinement and testing to establish their utility in assessing pharmacologic and nonpharmacologic treatment responses.

FUTURE CONSIDERATIONS FOR DAT DIAGNOSIS

The most careful application of clinical diagnostic criteria still results in uncertainty. The issues of diagnostic uncertainty lead to the question of how to determine the actual diagnosis. Autopsy is the only means available for establishing the type of dementia. Diagnostic clarification by autopsy is important for the patient's family members, as well as for the advancement of research into the cause and treatment of Alzheimer's disease and the other dementias. Currently, there is no clinical justification for a biopsy in AD for diagnostic purposes. However, future successful treatments may change our views. For research purposes, diagnostic certainty is important to support epidemiological, etiological, and prevention studies. At the present time, the clinical diagnosis of DAT has an accuracy of about 90% in uncomplicated cases, and this rate compares favorably with many other medical diagnoses where definitive tests are not available. For example, for appendicitis, a lower error rate than 10% at surgical pathology indicates that some cases may have been missed and is considered poor practice. Cerebrospinal fluid analyses and computer analyses on anatomical and functional brain images may soon give us more accurate diagnoses.

In the future, research must focus on prevention and early intervention. Accordingly, the clinical diagnosis of DAT must be made during the preclinical phase of this disease. Several recent studies have suggested that Alzheimer's disease can be predicted up to 4 years before a clinical diagnosis can be made (Masur et al., 1994; Petersen et al., 1995). Efficient recognition of preclinical Alzheimer's disease might be achieved by computer tests of cognition or more focused psychological tests until specific biological markers are developed.

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