can likewise reproduce the clinical syndrome of cortical or striatal injury.

THE CAUSES OF DEMENTIA

The single strongest risk factor for dementia is increasing age. The prevalence of disabling memory loss increases with each decade over age 50 and is usually associated with the microscopic changes of AD at autopsy. Yet some centenarians have intact memory function and no evidence of clinically significant dementia. Whether dementia is an inevitable consequence of normal human aging remains controversial.

The many causes of dementia are listed in Table 35-1. The frequency of each condition depends on the age group under study, access of the group to medical care, country of origin, and perhaps racial or ethnic background. AD is the most common cause of dementia in Western countries, accounting for more than half of all patients. Vascular disease is considered the second most frequent cause for dementia and is particularly common in elderly patients or populations with limited access to medical care, where vascular risk factors are undertreated. Often, vascular brain injury is mixed with neurodegenerative disorders, making it difficult, even for the neuropathologist, to estimate the contribution of cerebrovascular disease to the cognitive disorder in an individual patient. Dementias associated with Parkinson's disease (PD) (Chap. 449) are common and may develop years after onset of a parkinsonian disorder, as seen with PD-related dementia (PDD), or can occur concurrently with or preceding the motor syndrome, as in dementia with Lewy bodies (DLB). In patients under the age of 65, FTD rivals AD as the most common cause of dementia. Chronic intoxications, including those resulting from alcohol and prescription drugs, are an important and often treatable cause of dementia. Other disorders listed in Table 35-1 are uncommon but important because many are reversible. The classification of dementing illnesses into reversible and irreversible disorders is a useful approach to differential diagnosis. When effective treatments for the neurodegenerative conditions emerge, this dichotomy will become obsolete.

TABLE 35-1 DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Most Common Causes of Dementia	
Alzheimer's disease	Alcoholism[a]
Vascular dementia	PDD/LBD spectrum
Multi-infarct	Drug/medication intoxication[a]
Diffuse white matter disease (Binswanger's)	
Less Common Causes of Dementia	
Vitamin deficiencies	Toxic disorders
Thiamine (B_1): Wernicke's encephalopathy[a]	Drug, medication, and narcotic poisoning[a]
B_{12} (subacute combined degeneration)[a]	Heavy metal intoxication[a]
Nicotinic acid (pellagra)[a]	Organic toxins
Endocrine and other organ failure	Psychiatric
Hypothyroidism[a]	Depression (pseudodementia)[a]
Adrenal insufficiency and Cushing's syndrome[a]	Schizophrenia[a]
Hypo- and hyperparathyroidism[a]	Conversion disorder[a]
Renal failure[a]	Degenerative disorders
Liver failure[a]	Huntington's disease
Pulmonary failure[a]	Multisystem atrophy
Chronic infections	Hereditary ataxias (some forms)
HIV	Frontotemporal lobar degeneration spectrum
Neurosyphilis[a]	Multiple sclerosis
Papovavirus (JC virus) (progressive multifocal leukoencephalopathy)	Adult Down's syndrome with Alzheimer's disease
Tuberculosis, fungal, and protozoal[a]	ALS-parkinsonism-dementia complex of Guam
Whipple's disease[a]	Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases)
Head trauma and diffuse brain damage	Miscellaneous
Chronic traumatic encephalopathy	Sarcoidosis[a]
Chronic subdural hematoma[a]	Vasculitis[a]
Postanoxia	CADASIL, etc.
Postencephalitis	Acute intermittent porphyria[a]
Normal-pressure hydrocephalus[a]	Recurrent nonconvulsive seizures[a]
Intracranial hypotension	Additional conditions in children or adolescents
Neoplastic	Pantothenate kinase–associated neurodegeneration
Primary brain tumor[a]	Subacute sclerosing panencephalitis
Metastatic brain tumor[a]	Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)
Paraneoplastic/autoimmune limbic encephalitis[a]	

[a]Potentially reversible dementia.

Abbreviations: ALS, amyotrophic lateral sclerosis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBD, Lewy body disease; PDD, Parkinson's disease dementia.

In a study of 1000 persons attending a memory disorders clinic, 19% had a potentially reversible cause of the cognitive impairment and 23% had a potentially reversible concomitant condition that may have contributed to the patient's impairment. The three most common potentially reversible diagnoses were depression, normal pressure hydrocephalus (NPH), and alcohol dependence; medication side effects are also common and should be considered in every patient (Table 35-1).

Subtle cumulative decline in episodic memory is a common part of aging. This frustrating experience, often the source of jokes and humor, is referred to as *benign forgetfulness of the elderly*. *Benign* means that it is not so progressive or serious that it impairs reasonably successful and productive daily functioning, although the distinction between benign and more significant memory loss can be difficult to make. At age 85, the average person is able to learn and recall approximately one-half of the items (e.g., words on a list) that he or she could at age 18. A measurable cognitive problem that does not seriously disrupt daily activities is often referred to as *mild cognitive impairment* (MCI). Factors that predict progression from MCI to an AD dementia include a prominent memory deficit, family history of dementia, presence of an apolipoprotein ε4 (Apo ε4) allele, small hippocampal volumes, an AD-like signature of cortical atrophy, low cerebrospinal fluid Aβ, and elevated tau or evidence of brain amyloid deposition on positron emission tomography (PET) imaging.

The major degenerative dementias include AD, DLB, FTD and related disorders, HD, and prion diseases, including Creutzfeldt-Jakob disease (CJD). These disorders are all associated with the abnormal aggregation of a specific protein: $A\beta_{42}$ and tau in AD; α-synuclein in DLB; tau, TAR DNA-binding protein of 43 kDa (TDP-43), or *fu*sed in *s*arcoma (FUS) in FTD; huntingtin in HD; and misfolded prion protein (PrP^{sc}) in CJD (Table 35-2).

APPROACH TO THE PATIENT: Dementias

Three major issues should be kept at the forefront: (1) What is the best fit for a clinical diagnosis? (2) What component of the dementia syndrome is treatable or reversible? (3) Can the physician help to alleviate the burden on caregivers? A broad overview of the approach to dementia is shown in Table 35-3. The major degenerative dementias can usually be distinguished by the initial symptoms; neuropsychological, neuropsychiatric, and neurologic findings; and neuroimaging features (Table 35-4).

HISTORY

The history should concentrate on the onset, duration, and tempo of progression. An acute or subacute onset of confusion may be due to delirium (Chap. 34) and should trigger the search for intoxication, infection, or metabolic derangement. An elderly person