26 - 21 Neurocognitive Disorders

01 - 21.1 Introduction and Overview

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Neurocognitive Disorders 21.1 Introduction and Overview Advances in molecular biology diagnostic techniques and medication management have significantly improved the ability to recognize and treat cognitive disorders. Cognition includes memory, language, orientation, judgment, conducting interpersonal relationships, performing actions (praxis), and problem solving. Cognitive disorders reflect disruption in one or more of these domains and are frequently complicated by behavioral symptoms. Cognitive disorders exemplify the complex interface among neurology, medicine, and psychiatry in that medical or neurological conditions often lead to cognitive disorders that, in turn, are associated with behavioral symptoms. It can be argued that of all psychiatric conditions, cognitive disorders best demonstrate how biological insults result in behavioral symptomatology. The clinician must carefully assess the history and context of the presentation of these disorders before arriving at a diagnosis and treatment plan. This century-old distinction between organic and functional disorders is outdated and has been deleted from the nomenclature. Every psychiatric disorder has an organic (i.e., biological or chemical) component. Because of this reassessment, the concept of functional disorders has been determined to be misleading, and the term functional and its historical opposite, organic, are no longer used in the current Diagnostic and Statistical Manual of Mental Disorders (DSM) nomenclature. A further indication that the dichotomy is no longer valid is the revival of the term neuropsychiatry, which emphasizes the somatic substructure on which mental operations and emotions are based; it is concerned with the psychopathological accompaniments of brain dysfunction as observed in seizure disorders, for example. Neuropsychiatry focuses on the psychiatric aspects of neurological disorders and the role of brain dysfunction in psychiatric disorders. Cognitive disorders tend to defy Occam’s razor, challenging clinicians and nosologists with multiplicity, comorbidity, and unclear boundaries. These concerns are most true in elderly adults, the demographic group most at risk for cognitive disorders. Dementias of late life are particularly problematic in this regard. Existing, although often unrecognized, dementia is a major risk factor for superimposed delirium. Moreover, certain dementias, such as dementia with Lewy bodies or late stages of Alzheimer’s disease, may have chronic clinical presentations virtually indistinguishable from delirium except for temporal onset and the lack of an identifiable acute source. Similarly, the course of nearly all subjects developing a progressive dementia is complicated by the onset of one or more distinct behavioral syndromes,

including

anxiety, depression, sleep problems, psychosis, and aggression. These symptoms can be as distressing and disabling as the primary cognitive disorder. Some of these behavioral syndromes, such as psychosis, may themselves result from independent underlying biologies and may be additive with the primary neurodegenerative process. The boundaries between types of dementia and between dementia and normal aging can be similarly diffuse. Neuropathologic studies of both clinical and population samples have revealed a surprising truth. The most common neuropathologic presentation associated with dementia reveal mixtures of Alzheimer's disease, vascular, and Lewy body pathologies. Pure syndromes are relatively less common, although often the dementia is ascribed to one of the coexisting pathologies. Strategies regarding how to understand or reconcile multiple pathologies in the clinic are needed, although they lag behind. DEFINITION Delirium Delirium is marked by short-term confusion and changes in cognition. There are four subcategories based on several causes: (1) general medical condition (e.g., infection), (2) substance induced (e.g., cocaine, opioids, phencyclidine [PCP]), (3) multiple causes (e.g., head trauma and kidney disease), and (4) other or multiple etiologies (e.g., sleep deprivation, mediation). Delirium is discussed in Section 21.2. Dementia (Major Neurocogntive Disorder) Dementia, also referred to as major neurocognitive disorder in the fifth edition of DSM (DSM-5), is marked by severe impairment in memory, judgment, orientation, and cognition. The subcategories are (1) dementia of the Alzheimer's type, which usually occurs in persons older than 65 years of age and is manifested by progressive intellectual disorientation and dementia, delusions, or depression; (2) vascular dementia, caused by vessel thrombosis or hemorrhage; (3) human immunodeficiency virus (HIV) disease; (4) head trauma; (5) Pick's disease or frontotemporal lobar degeneration; (6) Prion disease such as Creutzfeldt-Jakob disease, which is caused by a slow-growing transmittable virus); (7) substance induced, caused by toxin or medication (e.g., gasoline fumes, atropine); (8) multiple etiologies; and (9) not specified (if cause is unknown). In DSM-5, a less severe form of dementia called mild neurocognitive disorder is listed. Dementia is discussed in Section 21.3. Amnestic Disorder Amnestic disorders are classified in DSM-5 as major neurocognitive disorders caused by other medical conditions. They are marked primarily by memory impairment in addition to other cognitive symptoms. They may be caused by (1) medical conditions (hypoxia),

(2) toxins or medications (e.g., marijuana, diazepam), and (3) unknown causes. These disorders are discussed in Section 21.4. CLINICAL EVALUATION During the history taking, the clinician seeks to elicit the development of the illness. Subtle cognitive disorders, fluctuating symptoms, and progressing disease processes may be tracked effectively. The clinician should obtain a detailed rendition of changes in the patient's daily routine involving such factors as self-care, job responsibilities, and work habits; meal preparation; shopping and personal support; interactions with friends; hobbies and sports; reading interests; religious, social, and recreational activities; and ability to maintain personal finances. Understanding the past life of each patient provides an invaluable source of baseline data regarding changes in function, such as attention and concentration, intellectual abilities, personality, motor skills, and mood and perception. The examiner seeks to find the particular pursuits that the patient considers most important, or central, to his or her lifestyle and attempts to discern how those pursuits have been affected by the emerging clinical condition. Such a method provides the opportunity to appraise both the impact of the illness and the patientspecific baseline for monitoring the effects of future therapies. Mental

Status Examination After taking a thorough history, the clinician's primary tool is the assessment of the patient's mental status. As with the physical examination, the mental status examination is a means of surveying functions and abilities to allow a definition of personal strengths and weakness. It is a repeatable, structured assessment of symptoms and signs that promotes effective communication among clinicians. It also establishes the basis for future comparison, essential for documenting therapeutic effectiveness, and it allows comparisons between different patients, with a generalization of findings from one patient to another. Table 21.1-1 lists the components of a comprehensive neuropsychiatric mental status examination. Table 21.1-1 Neuropsychiatric Mental Status Examination

Cognition When testing cognitive functions, the clinician should evaluate memory; visuospatial and constructional abilities; and reading, writing, and mathematical abilities. Assessment of abstraction ability is also valuable, although a patient's performance on tasks such as proverb interpretation may be a useful bedside projective test in some patients, the specific interpretation may result from a variety of factors, such as poor education, low intelligence, and failure to understand the concept of proverbs, as well as from a broad array of primary and secondary psychopathological disturbances. PATHOLOGY AND LABORATORY EXAMINATION As with all medical tests, psychiatric evaluations such as the mental status examination must be interpreted in the overall context of thorough clinical and laboratory assessment. Psychiatric and neuropsychiatric patients require careful physical examination, especially when issues exist that involve etiologically related or comorbid medical conditions. When consulting internists and other medical specialists, the clinician must ask specific questions to focus the differential diagnostic process and use the consultation most effectively. In particular, most systemic medical or primary cerebral diseases that lead to psychopathological disturbances also manifest with a variety of peripheral or central abnormalities. A screening laboratory evaluation is sought initially and may be followed by a variety of ancillary tests to increase the diagnostic specificity. Table 21.1-2 lists such procedures,

some of which are described below. Table 21.1-2 Screening Laboratory Tests ELECTROENCEPHALOGRAPHY Electroencephalography (EEG) is an easily accessible, noninvasive test of brain dysfunction that has high sensitivity for many disorders but relatively low specificity. Beyond its recognized uses in epilepsy, EEG's greatest utility is in detecting altered electrical rhythms associated with mild delirium, space-occupying lesions, and continuing complex partial seizures (in which the patient remains conscious, although behaviorally impaired). EEG is also sensitive to metabolic and toxic

states, often showing a diffuse slowing of brain activity. The EEG is discussed in Section 3.4, Electrophysiology. COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING Computed tomography (CT) and magnetic resonance imaging (MRI) have proved to be powerful neuropsychiatric research tools. Recent developments in MRI allow the direct measurement of structures such as the thalamus, basal ganglia, hippocampus, and amygdala, as well as temporal and apical areas of the brain and the structures of the posterior fossa. MRI has largely replaced CT as the most utilitarian and cost-effective method of imaging in neuropsychiatry. Patients with acute cerebral hemorrhages or hematomas must continue to be assessed using CT, but these patients present infrequently in psychiatric settings. MRI better discriminates the interface between gray and white matter and is useful in detecting a variety of white matter lesions in the periventricular and subcortical regions. The pathophysiological significance of such findings remains to be defined.

White matter abnormalities are detected in younger patients with multiple sclerosis or human immunodeficiency virus (HIV) infection and in older patients with hypertension, vascular dementia, or dementia of the Alzheimer's type. The prevalence of these abnormalities is also increased in healthy, aging individuals who have no defined disease process. As with CT, the greatest utility of MRI in the evaluation of patients with dementia arises from what it may exclude (tumors, vascular disease) rather than what it can demonstrate specifically. BRAIN BIOPSY Brain needle biopsy is used to diagnose a variety of disorders: Alzheimers disease, autoimmune encephalopaties, and tumors. It is conducted stereotactically and indicated when no other investigative techniques such as MRI or lumbar puncture have been sufficient to make a diagnosis. The procedure is not without risk in that seizures may occur if scar tissue forms at the biopsy site. NEUROPSYCHOLOGICAL TESTING Neuropsychological testing provides a standardized, quantitative, reproducible evaluation of a patient's cognitive abilities. Such procedures may be useful for initial evaluation and periodic assessment. Tests are available that assess abilities across the broad array of cognitive domains, and many offer comparative normative groups or adjusted scores based on normative samples. The clinician seeking neuropsychological consultation should understand enough about the strengths and weaknesses of selected procedures to benefit fully from the results obtained. REFERENCES Balzer D. Neurocognitive disorders in DSM-5. Am J Psych. 2013;170:585. Blanc-Lapierre A, Bouvier G, Gruber A, Leffondré K, Lebailly P, Fabrigoule C, Baldi I. Cognitive disorders and occupational exposure to organophosphates: Results from the PHYTONER Study. Am J Epidemiol. 2013;177:1086. Bugnicourt J-M, Godefroy O, Chillon J-M, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: The neglected kidney-brain axis. J Am Soc Nephrol. 2013;24:353. Bugnicourt J-M, Guegan-Massardier E, Roussel M, Martinaud O, Canaple S, Triquenot-Bagan A, Wallon D, Lamy C, Leclercq C, Hannequin D, Godefroy O. Cognitive impairment after cerebral venous thrombosis: A two-center study. J Neurol. 2013;260:1324.

02 - 21.2 Delirium

21.2 Delirium

Fields J, Dumaop W, Langford TD, Rockenstein E, Masliah E. Role of neurotrophic factor alterations in the neurodegenerative process in HIV associated neurocognitive disorders. J Neuroimmune Pharmacol. 2014;9(2):102–116. Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain. 2008;131:665. Launer LJ. Epidemiologic insight into blood pressure and cognitive disorders. In: Yaffe K, ed. Chronic Medical Disease and Cognitive Aging: Toward a Healthy Body and Brain. New York: Oxford University Press; 2013:1. Mayeux R, Reitz C, Brickman AM, Haan MN, Manly JJ, Glymour MM, Weiss CC, Yaffe K, Middleton L, Hendrie HC, Warren LH, Hayden KM, Welsh-Bohmer KA, Breitner JCS, Morris JC. Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment—Part 1. Alzheimer's Demen. 2011;7:15. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in communitydwelling older persons. Neurology. 2007;69:2197. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol. 2007;62:406. Sweet RA. Cognitive disorders: Introduction. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia Lippincott Williams & Wilkins; 2009:1152. Verdelho A, Madureira S, Moleiro C, Ferro JM, Santos CO, Erkinjuntti T, Pantoni L, Fazekas F, Visser M, Waldemar G, Wallin A, Hennerici M, Inzitari D. White matter changes and diabetes predict cognitive decline in the elderly: The LADIS study. Neurology. 2010;75(2):160. Weiner MF. Cognitive disorders as psychobiological processes. In: Weiner MF, Lipton AM. The American Psychiatric Publishing Textbook of Alzheimer Disease and Other Dementias. Arlington, VA: American Psychiatric Publishing; 2009:137. Zarit SH, Zarit JM. Disorders of aging: Delirium, dementia and other cognitive problems. In: Zarit SH, Zarit JM. Mental Disorders in Older Adults: Fundamentals of Assessment and Treatment. 2nd ed. New York: Guilford Press; 2007:40. 21.2 Delirium Delirium is characterized by an acute decline in both the level of consciousness and cognition with particular impairment in attention. A life threatening, yet potentially reversible disorder of the central nervous system (CNS), delirium often involves perceptual disturbances, abnormal psychomotor activity, and sleep cycle impairment. Delirium is often underrecognized by health care workers. Part of the problem is that the syndrome has a variety of other names (Table 21.2-1). Table 21.2-1 Delirium by Other Names

The hallmark symptom of delirium is an impairment of consciousness, usually occurring in association with global impairments of cognitive functions. Abnormalities of mood, perception, and behavior are common psychiatric symptoms. Tremor, asterixis, nystagmus, incoordination, and urinary incontinence are common neurological symptoms. Classically, delirium has a sudden onset (hours or days), a brief and fluctuating course, and rapid improvement when the causative factor is identified and eliminated, but each of these characteristic features can vary in individual patients.

Physicians must recognize delirium to identify and treat the underlying cause and to avert the development of delirium-related complications such as accidental injury because of the patient's clouded consciousness. EPIDEMIOLOGY Delirium is a common disorder, with most incidence and prevalence rates reported in elderly adults. In community studies, 1 percent of elderly persons age 55 years or older have delirium (13 percent in the age 85 years and older group in the community). Among elderly emergency department patients, 5 to 10 percent have been reported to have delirium. At the time of admission to medical wards, between 15 and 21 percent of older patients meet criteria for delirium-prevalent cases. Of patients free of delirium at time of hospital admission, 5 to 30 percent reported subsequent incidences of delirium during hospitalization. Delirium has been reported in 10 to 15 percent of general surgical patients, 30 percent of open heart surgery patients, and more than 50 percent of patients treated for hip fractures. Delirium occurs in 70 to 87 percent of those in intensive care units and in up to 83 percent of all patients at the end of life care. Sixty percent of patients in nursing homes or postacute care settings have delirium. An estimated 21 percent of patients with severe burns and 30 to 40 percent of patients with acquired immune deficiency syndrome (AIDS) have episodes of delirium while they are hospitalized. Delirium develops in 80 percent of terminally ill patients. The causes of postoperative delirium include the stress of surgery, postoperative pain, insomnia, pain medication, electrolyte imbalances, infection, fever, and blood loss. The incidence and prevalence rates for delirium across settings are shown in Table 21.2-2. Table 21.2-2 Delirium Incidence and Prevalence in Multiple Settings

Risk for delirium could be conceptualized into two categories, predisposing and precipitating factors (Tables 21.2-3 and 21.2-4). Current approaches to delirium focus primarily on the precipitation factors and do little to address the predisposing factors. Managing predisposing factors for delirium becomes essential in decreasing future episodes of delirium and the morbidity and mortality associated with it. Table 21.2-4 Precipitating Factors for Delirium

Table 21.2-3 Predisposing Factors for Delirium

Advanced age is a major risk factor for the development of delirium. Approximately 30 to 40 percent of hospitalized patients older than age 65 years have an episode of delirium, and another 10 to 15 percent of elderly persons exhibit delirium on admission to the hospital. Of nursing home residents older than age 75 years, 60 percent have repeated episodes of delirium. Male gender is also an independent risk factor for delirium. Delirium is a poor prognostic sign. Rates of institutionalization are increased threefold for patients 65 years and older who exhibit delirium while in the hospital. The 3-month mortality rate of patients who have an episode of delirium is estimated to be 23 to 33 percent. The 1-year mortality rate for patients who have an episode of delirium may be as high as 50 percent. Elderly patients who experience delirium while hospitalized have a 21 to 75 percent mortality rate during that hospitalization. After discharge, up to 15 percent of these persons die within a 1-month period, and 25 percent die within 6 months. ETIOLOGY The major causes of delirium are CNS disease (e.g., epilepsy), systemic disease (e.g., cardiac failure), and either intoxication or withdrawal from pharmacological or toxic

agents (Table 21.2-5). When evaluating patients with delirium, clinicians should assume that any drug that a patient has taken may be etiologically relevant to the delirium. Table 21.2-5 Common Causes of Delirium

DIAGNOSIS AND CLINICAL FEATURES The DSM-5 diagnostic criteria for delirium are listed in Table 21.2-6. The syndrome of delirium is almost always caused by one or more systemic or cerebral derangements that affect brain function. Table 21.2-6 DSM-5 Diagnostic Criteria for Delirium

A 70-year old woman, Mrs. K, was brought to the emergency department by the police. The police had responded to complaints from neighbors that Mrs. K was wandering the neighborhood and was not taking care of herself. When the police found Mrs. K in her apartment, she was dirty, foul smelling, and wearing nothing but a bra. Her apartment was also filthy with garbage and rotting food everywhere. When interviewed, Mrs. K would not look at the interviewer and was confused and unresponsive to most of the questions asked. She knew her name and address but not the date. She was unable to describe the events that led to her admission. The next day, the supervising psychiatrist attempted to interview Mrs. K. Her facial expression was still unresponsive, and she still did not know the month or the name of the hospital she was in. She explained that the neighbors called the police because she

was “sick” and that she did indeed feel sick and weak, with pains in her shoulder. She also reported not eating for 3 days. She denied ever being in a psychiatric hospital or hearing voices but acknowledged seeing a psychiatrist at one point because she had trouble sleeping. She said the doctor had prescribed medication, but she could not remember the name. The core features of delirium include altered consciousness, such as decreased level of consciousness; altered attention, which can include diminished ability to focus, sustain, or shift attention; impairment in other realms of cognitive function, which can manifest as disorientation (especially to time and space) and decreased memory; relatively rapid onset (usually hours to days); brief duration (usually days to weeks); and often marked, unpredictable fluctuations in severity and other clinical manifestations during the course of the day, sometimes worse at night (sundowning), which may range from periods of lucidity to severe cognitive impairment and disorganization. Associated clinical features are often present and may be prominent. They can include disorganization of thought processes (ranging from mild tangentiality to frank incoherence), perceptual disturbances such as illusions and hallucinations, psychomotor hyperactivity and hypoactivity, disruption of the sleep–wake cycle (often manifested as fragmented sleep at night, with or without daytime drowsiness), mood alterations (from subtle irritability to obvious dysphoria, anxiety, or even euphoria), and other manifestations of altered neurological function (e.g., autonomic hyperactivity or instability, myoclonic jerking, and dysarthria). The EEG usually shows diffuse slowing of background activity, although patients with delirium caused by alcohol or sedative– hypnotic withdrawal have low-voltage fast activity. The major neurotransmitter hypothesized to be involved in delirium is acetylcholine, and the major neuroanatomical area is the reticular formation. The reticular formation of the brainstem is the principal area regulating attention and arousal; the major pathway implicated in delirium is the dorsal tegmental pathway, which projects from the mesencephalic reticular formation to the tectum and thalamus. Several studies have reported that a variety of delirium-inducing factors result in decreased acetylcholine activity in the brain. One of the most common causes of delirium is toxicity from too many prescribed medications with anticholinergic activity. Researchers have suggested other pathophysiological mechanisms for delirium. In particular, the delirium associated with alcohol withdrawal has been associated with hyperactivity of the locus ceruleus and its noradrenergic neurons. Other neurotransmitters that have been implicated are serotonin and glutamate. PHYSICAL AND LABORATORY EXAMINATIONS Delirium is usually diagnosed at the bedside and is characterized by the sudden onset of

symptoms. A bedside mental status examination—such as the Mini-Mental State Examination, the mental status examination, or neurological signs—can be used to document the cognitive impairment and to provide a baseline from which to measure

the patient's clinical course. The physical examination often reveals clues to the cause of the delirium (Table 21.2-7). The presence of a known physical illness or a history of head trauma or alcohol or other substance dependence increases the likelihood of the diagnosis. Table 21.2-7 Physical Examination of the Delirious Patient

The laboratory workup of a patient with delirium should include standard tests and additional studies indicated by the clinical situation (Table 21.2-8). In delirium, the EEG characteristically shows a generalized slowing of activity and may be useful in differentiating delirium from depression or psychosis. The EEG of a delirious patient

sometimes shows focal areas of hyperactivity. In rare cases, it may be difficult to differentiate delirium related to epilepsy from delirium related to other causes. Table 21.2-8 Laboratory Workup of the Patient with Delirium DIFFERENTIAL DIAGNOSIS Delirium versus Dementia A number of clinical features help distinguish delirium from dementia (Table 21.2-9). The major differential points between dementia and delirium are the time to development of the condition and the fluctuation in level of attention in delirium compared with relatively consistent attention in dementia. The time to development of symptoms is usually short in delirium, and except for vascular dementia caused by stroke, it is usually gradual and insidious in dementia. Although both conditions include cognitive impairment, the changes in dementia are more stable over time and, for example, usually do not fluctuate over the course of a day. A patient with dementia is usually alert; a patient with delirium has episodes of decreased consciousness. Occasionally, delirium occurs in a patient with dementia, a condition known as beclouded dementia. A dual diagnosis of delirium can be made when there is a definite history of preexisting dementia. Table 21.2-9 Frequency of Clinical Features of Delirium Contrasted with Dementia

Delirium versus Schizophrenia or Depression Delirium must also be differentiated from schizophrenia and depressive disorder. Some patients with psychotic disorders, usually schizophrenia or manic episodes, can have periods of extremely disorganized behavior difficult to distinguish from delirium. In general, however, the hallucinations and delusions of patients with schizophrenia are more constant and better organized than those of patients with delirium. Patients with schizophrenia usually experience no change in their level of consciousness or in their orientation. Patients with hypoactive symptoms of delirium may appear somewhat similar to severely depressed patients, but they can be distinguished on the basis of an EEG. Other psychiatric diagnoses to consider in the differential diagnosis of delirium are brief psychotic disorder, schizophreniform disorder, and dissociative disorders. Patients with factitious disorders may attempt to simulate the symptoms of delirium but usually reveal the factitious nature of their symptoms by inconsistencies on their mental status examinations, and an EEG can easily separate the two diagnoses. COURSE AND PROGNOSIS Although the onset of delirium is usually sudden, prodromal symptoms (e.g., restlessness and fearfulness) can occur in the days preceding the onset of florid symptoms. The symptoms of delirium usually persist as long as the causally relevant factors are present, although delirium generally lasts less than 1 week. After identification and removal of the causative factors, the symptoms of delirium usually recede over a 3- to 7-day

period, although some symptoms may take up to 2 weeks to resolve completely. The older the patient and the longer the patient has been delirious, the longer the delirium takes to resolve. Recall of what transpired during a delirium, once it is over, is characteristically spotty; a patient may refer to the episode as a bad dream or a nightmare only vaguely remembered. As stated in the discussion on epidemiology, the occurrence of delirium is associated with a high mortality rate in the ensuing year, primarily because of the serious nature of the associated medical conditions that lead to delirium. Whether delirium progresses to dementia has not been demonstrated in carefully controlled studies, although many clinicians believe that they have seen such a

progression. A clinical observation that has been validated by some studies, however, is that periods of delirium are sometimes followed by depression or posttraumatic stress disorder. TREATMENT In treating delirium, the primary goal is to treat the underlying cause. When the underlying condition is anticholinergic toxicity, the use of physostigmine salicylate (Antilirium), 1 to 2 mg intravenously or intramuscularly, with repeated doses in 15 to 30 minutes may be indicated. The other important goal of treatment is to provide physical, sensory, and environmental support. Physical support is necessary so that delirious patients do not get into situations in which they may have accidents. Patients with delirium should be neither sensory deprived nor overly stimulated by the environment. They are usually helped by having a friend or relative in the room or by the presence of a regular sitter. Familiar pictures and decorations; the presence of a clock or a calendar; and regular orientations to person, place, and time help make patients with delirium comfortable. Delirium can sometimes occur in older patients wearing eye patches after cataract surgery (“black-patch delirium”). Such patients can be helped by placing pinholes in the patches to let in some stimuli or by occasionally removing one patch at a time during recovery. Pharmacotherapy The two major symptoms of delirium that may require pharmacological treatment are psychosis and insomnia. A commonly used drug for psychosis is haloperidol (Haldol), a butyrophenone antipsychotic drug. Depending on a patient’s age, weight, and physical condition, the initial dose may range from 2 to 6 mg intramuscularly, repeated in an hour if the patient remains agitated. As soon as the patient is calm, oral medication in liquid concentrate or tablet form should begin. Two daily oral doses should suffice, with two-thirds of the dose being given at bedtime. To achieve the same therapeutic effect, the oral dose should be approximately 1.5 times the parenteral dose. The effective total daily dose of haloperidol may range from 5 to 40 mg for most patients with delirium. Haloperidol has been associated with prolongation of QT interval. Clinicians should evaluate baseline and periodic electrocardiograms as well as monitor cardiac status of the patient. Droperidol (Inapsine) is a butyrophenone available as an alternative intravenous (IV) formulation, although careful monitoring of the electrocardiogram may be prudent with this treatment. The U.S. Food and Drug Administration (FDA) has issued a Black Box Warning because cases of QT prolongation and torsades de pointes have been reported in patients receiving droperidol. Because of its potential for serious proarrhythmic effects and death, it should be used only in patients who do not respond well to other treatments. Phenothiazines should be avoided in delirious patients because these drugs are associated with significant anticholinergic activity. Use of second-generation antipsychotics, such as risperidone (Risperdal), clozapine, olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), and aripiprazole

(Abilify), may be considered for delirium management, but clinical trial experience with these agents for delirium is limited. Ziprasidone appears to have an activating effect and may not be appropriate in delirium management. Olanzapine is available for intramuscular (IM) use and as a

rapidly disintegrating oral preparation. These routes of administration may be preferable for some patients with delirium who are poorly compliant with medications or who are too sedated to safely swallow medications. Insomnia is best treated with benzodiazepines with short or intermediate half-lives (e.g., lorazepam [Ativan] 1 to 2 mg at bedtime). Benzodiazepines with long half-lives and barbiturates should be avoided unless they are being used as part of the treatment for the underlying disorder (e.g., alcohol withdrawal). Clinicians should be aware that there is no conclusive evidence to support the use of benzodiazepines in non–alcoholrelated delirium. There have been case reports of improvement in or remission of delirious states caused by intractable medical illnesses with electroconvulsive therapy (ECT); however, routine consideration of ECT for delirium is not advised. If delirium is caused by severe pain or dyspnea, a physician should not hesitate to prescribe opioids for both their analgesic and sedative effects (Table 21.2-10). Table 21.2-10 Pharmacological Treatment Current trials are ongoing to see if dexmedetomidine (Precedex) is a more effective medication than haloperidol in the treatment of agitation and delirium in patients receiving mechanical ventilation in an intensive care unit. Treatment in Special Populations Parkinson’s Disease. In Parkinson’s disease, the antiparkinsonian agents are frequently implicated in causing delirium. If a coexistent dementia is present, delirium is twice as likely to develop in patients with Parkinson’s disease with dementia receiving antiparkinsonian agents than in those without dementia. Decreasing the dosage of the antiparkinsonian agent has to be weighed against a worsening of motor symptoms. If the antiparkinsonian agents cannot be further reduced, or if the delirium persists after attenuation of the antiparkinsonian agents, clozapine is recommended. If a patient is

not able to tolerate clozapine or the required blood monitoring, alternative antipsychotic agents should be considered. Quetiapine has not been as rigorously studied as clozapine and may have parkinsonian side effects, but it is used in clinical practice to treat psychosis in Parkinson’s disease. Terminally Ill Patients. When delirium occurs in the context of a terminal illness, issues about advanced directives and the existence of a health care proxy become more significant. This scenario emphasizes the importance of early development of advance directives for health care decision making while a person has the capacity to communicate the wishes regarding the extent of aggressive diagnostic tests at life’s end. The focus may change from an aggressive search for the etiology of the delirium to one of palliation, comfort, and assistance with dying. REFERENCES Caraceni A, Grassi L. Delirium: Acute Confusional States in Palliative Medicine. 2nd ed. New York: Oxford University Press; 2111. Franco JG, Trzepacz PT, Meagher DJ, Kean J, Lee Y, Kim J-L, Kishi Y, Furlanetto LM, Negreiros D, Huang M-C, Chen C-H, Leonard M, de Pablo J. Three core domains of delirium validated using exploratory and confirmatory factor analyses. Psychosomatics. 2113;54:227. Hosie A, Davidson PM, Agar M, Sanderson CR, Philips J. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: A systematic review. Palliative Med. 2113;27:486. Juliebö V, Björo K, Krogseth M, Skovlund E, Ranhoff AH, Wyller TB. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. J Am Geriatr Soc. 2109;57:1354. Kiely DK, Marcantonio ER, Inouye SK, Shaffer ML, Bergmann MA, Yang FM, Fearing MA, Jones RN. Persistent delirium predicts greater mortality. J Am Geriatr Soc. 2109;57:55. Maldonado JR, Wysong A, van der Starre PJA, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics. 2109;50:216. Morandi A, McCurley J, Vasilevskis EE. Tools to detect delirium superimposed on dementia: A systematic review: Erratum. J Am Ger Soc. 2113;61:174. O’Mahony R, Murthy L, Akunne A, Young J. Synopsis of the National Institute for Health and Clinical Excellence

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03 - 21.3 Dementia (Major Neurocognitive Disorder)

21.3 Dementia (Major Neurocognitive Disorder)

Yang FM, Marcantonio ER, Inouye SK, Kiely DK, Rudolph JL, Fearing MA, Jones RN. Phenomenological subtypes of delirium in older persons: Patterns, prevalence, and prognosis. Psychosomatics. 2109;50:248. 21.3 Dementia (Major Neurocognitive Disorder) Dementia refers to a disease process marked by progressive cognitive impairment in clear consciousness. Dementia does not refer to low intellectual functioning or mental retardation because these are developmental and static conditions, and the cognitive deficits in dementia represent a decline from a previous level of functioning. Dementia involves multiple cognitive domains and cognitive deficits cause significant impairment in social and occupational functioning. There are four types of dementias based on etiology: Alzheimer’s disease, dementia of Lewy bodies, vascular dementia, frontotemporal dementia, traumatic brain injury (TBI), HIV, prion disease, Parkinson’s disease, and Huntington’s disease. Dementia can also be caused by other medical and neurological conditions or can be caused by various substances. (See Section 21.4: Amnestic Disorders.) The critical clinical points of dementia are the identification of the syndrome and the clinical workup of its cause. The disorder can be progressive or static; permanent or reversible. An underlying cause is always assumed, although, in rare cases, it is impossible to determine a specific cause. The potential reversibility of dementia is related to the underlying pathological condition and to the availability and application of effective treatment. Approximately 15 percent of people with dementia have reversible illnesses if treatment is initiated before irreversible damage takes place. EPIDEMIOLOGY With the aging population, the prevalence of dementia is rising. The prevalence of moderate to severe dementia in different population groups is approximately 5 percent in the general population older than 65 years of age, 20 to 40 percent in the general population older than 85 years of age, 15 to 20 percent in outpatient general medical practices, and 50 percent in chronic care facilities. Of all patients with dementia, 50 to 60 percent have the most common type of dementia, dementia of the Alzheimer’s type (Alzheimer’s disease). Dementia of the Alzheimer’s type increases in prevalence with increasing age. For persons age 65 years, men have a prevalence rate of 0.6 percent and women of 0.8 percent. At age 90, rates are 21 percent. For all of these figures, 40 to 60 percent of cases are moderate to severe. The rates of prevalence (men to women) are 11 and 14 percent at age 85, 21 and 25 percent at age 90 years and 36 and 41 percent at age 95 years. Patients with dementia of the Alzheimer’s type occupy more than 50

percent of nursing home beds. More than 2 million persons with dementia are cared for in these homes. By 2050, current predictions suggest that there will be 14 million Americans with Alzheimer's disease and therefore more than 18 million people with dementia. The second most common type of dementia is vascular dementia, which is causally

related to cerebrovascular diseases. Hypertension predisposes a person to the disease. Vascular dementias account for 15 to 30 percent of all dementia cases. Vascular dementia is most common in persons between the ages of 60 and 70 and is more common in men than in women. Approximately 10 to 15 percent of patients have coexisting vascular dementia and dementia of the Alzheimer's type. Other common causes of dementia, each representing 1 to 5 percent of all cases, include head trauma; alcohol-related dementias; and various movement disorder-related dementias, such as Huntington's disease and Parkinson's disease. Because dementia is a fairly general syndrome, it has many causes, and clinicians must embark on a careful clinical workup of a patient with dementia to establish its cause. ETIOLOGY The most common causes of dementia in individuals older than 65 years of age are (1) Alzheimer's disease, (2) vascular dementia, and (3) mixed vascular and Alzheimer's dementia. Other illnesses that account for approximately 10 percent include Lewy body dementia; Pick's disease; frontotemporal dementias; normal-pressure hydrocephalus (NPH); alcoholic dementia; infectious dementia, such as HIV or syphilis; and Parkinson's disease. Many types of dementias evaluated in clinical settings can be attributable to reversible causes, such as metabolic abnormalities (e.g., hypothyroidism), nutritional deficiencies (e.g., vitamin B12 or folate deficiencies), or dementia syndrome caused by depression. See Table 21.3-1 for a review of possible etiologies of dementia. Table 21.3-1 Possible Etiologies of Dementia

Dementia of the Alzheimer's Type In 1907, Alois Alzheimer (Fig. 21.3-1) first described the condition that later assumed his name. He described a 51-year-old woman with a 4½-year course of progressive dementia. The final diagnosis of Alzheimer's disease requires a neuropathological examination of the brain; nevertheless, dementia of the Alzheimer's type is commonly diagnosed in the clinical setting after other causes of dementia have been excluded from diagnostic consideration.

FIGURE 21.3-1 Alois Alzheimer (1864–1915), a German psychiatrist, described a type of senile dementia that bears his name Genetic Factors. Although the cause of dementia of the Alzheimer's type remains unknown, progress has been made in understanding the molecular basis of the amyloid deposits that are a hallmark of the disorder's neuropathology. Some studies have indicated that as many as 40 percent of patients have a family history of dementia of the Alzheimer's type; thus, genetic factors are presumed to play a part in the development of the disorder, at least in some cases. Additional support for a genetic influence is the concordance rate for monozygotic twins, which is higher than the rate for dizygotic twins (43 percent vs. 8 percent, respectively). In several well-documented cases, the disorder has been transmitted in families through an autosomal dominant gene, although such transmission is rare. Alzheimer's type dementia has shown linkage to chromosomes 1, 14, and 21. AMYLOID PRECURSOR PROTEIN. The gene for amyloid precursor protein is on the long arm of chromosome 21. The process of differential splicing yields four forms of amyloid precursor protein. The β/A4 protein, the major constituent of senile plaques, is a 42amino acid peptide that is a breakdown product of amyloid precursor protein. In Down syndrome (trisomy 21) are found three copies of the amyloid precursor protein gene, and in a disease in which a mutation is found at codon 717 in the amyloid precursor

protein gene, a pathological process results in the excessive deposition of β/A4 protein. Whether the processing of abnormal amyloid precursor protein is of primary causative significance in Alzheimer's disease is unknown, but many research groups are studying both the normal metabolic processing of amyloid precursor protein and its processing in patients with dementia of the Alzheimer's type in an attempt to answer this question. MULTIPLE E4 GENES. One study implicated gene E4 in the origin of Alzheimer's disease.

People with one copy of the gene have Alzheimer's disease three times more frequently than do those with no E4 gene, and people with two E4 genes have the disease eight times more frequently than do those with no E4 gene. Diagnostic testing for this gene is not currently recommended because it is found in persons without dementia and not found in all cases of dementia. Neuropathology. The classic gross neuroanatomical observation of a brain from a patient with Alzheimer's disease is diffuse atrophy with flattened cortical sulci and enlarged cerebral ventricles. The classic and pathognomonic microscopic findings are senile plaques, neurofibrillary tangles, neuronal loss (particularly in the cortex and the hippocampus), synaptic loss (perhaps as much as 50 percent in the cortex), and granulovascular degeneration of the neurons. Neurofibrillary tangles (Fig. 21.3-2) are composed of cytoskeletal elements, primarily phosphorylated tau protein, although other cytoskeletal proteins are also present. Neurofibrillary tangles are not unique to Alzheimer's disease; they also occur in Down syndrome, dementia pugilistica (punchdrunk syndrome), Parkinson-dementia complex of Guam, Hallervorden-Spatz disease, and the brains of normal people as they age. Neurofibrillary tangles are commonly found in the cortex, the hippocampus, the substantia nigra, and the locus ceruleus.

FIGURE 21.3-2 Photomicrographs of Alzheimer's disease neuropathology. (A) Deposition of insoluble fibrillar Aβ into plaques begins in the neocortex, labeled here using an antibody against Aβ and appearing as reddish-brown deposits (arrows). (B) Bielchowsky stain of neocortex from an individual who died in advanced stages of Alzheimer's disease (Braak stage VI). The Aβ plaques appear as dark brown in this preparation (arrows) and can be seen to be associated with dystrophic neuronal processes (arrowheads) in which insoluble microtubule-associate protein τ (MAPT) aggregates appear as black deposits. This neurofibrillary pathology also appears extensively throughout the neuropil, and several neurofibrillary tangles can be seen (open arrowheads). (C) Bielchowsky stain of

neocortex from an individual who died in a less advanced disease stage (Braak stage IV). Although some neurofibrillary tangles are still evident (open arrowheads), the degree of neurofibrillary pathology in the neuropil is substantially diminished. (D) Isolated neurofibrillary tangles (open arrowheads) in entorhinal cortex that can be seen in normal aging (Bielchowsky stain). Notice the lack of Aβ plaques and limited neuropil involvement. (All images obtained at 200× magnification and provided courtesy of Dr. Ronald L. Hamilton, Department of Pathology, Division of Neuropathology, University of Pittsburgh School of Medicine.) Senile plaques, also referred to as amyloid plaques, more strongly indicate Alzheimer's disease, although they are also seen in Down syndrome and, to some extent, in normal aging. Senile plaques are composed of a particular protein, β/A4, and astrocytes, dystrophic neuronal processes, and microglia. The number and the density of senile plaques present in postmortem brains have been correlated with the severity of the disease that affected the persons. Neurotransmitters. The neurotransmitters that are most often implicated in the pathophysiological condition of Alzheimer's disease are acetylcholine and

norepinephrine, both of which are hypothesized to be hypoactive in Alzheimer's disease. Several studies have reported data consistent with the hypothesis that specific degeneration of cholinergic neurons is present in the nucleus basalis of Meynert in persons with Alzheimer's disease. Other data supporting a cholinergic deficit in Alzheimer's disease demonstrate decreased acetylcholine and choline acetyltransferase concentrations in the brain. Choline acetyltransferase is the key enzyme for the synthesis of acetylcholine, and a reduction in choline acetyltransferase concentration suggests a decrease in the number of cholinergic neurons present. Additional support for the cholinergic deficit hypothesis comes from the observation that cholinergic antagonists, such as scopolamine and atropine, impair cognitive abilities, whereas cholinergic agonists, such as physostigmine and arecoline, enhance cognitive abilities. Decreased norepinephrine activity in Alzheimer's disease is suggested by the decrease in norepinephrine-containing neurons in the locus ceruleus found in some pathological examinations of brains from persons with Alzheimer's disease. Two other neurotransmitters implicated in the pathophysiological condition of Alzheimer's disease are the neuroactive peptides somatostatin and corticotropin; decreased concentrations of both have been reported in persons with Alzheimer's disease. Other Causes. Another theory to explain the development of Alzheimer's disease is that an abnormality in the regulation of membrane phospholipid metabolism results in membranes that are less fluid—that is, more rigid—than normal. Several investigators are using molecular resonance spectroscopic imaging to assess this hypothesis directly in patients with dementia of the Alzheimer's type. Aluminum toxicity has also been hypothesized to be a causative factor because high levels of aluminum have been found in the brains of some patients with Alzheimer's disease, but this is no longer considered

a significant etiological factor. Excessive stimulation by the transmitter glutamate that may damage neurons is another theory of causation. Familial Multiple System Taupathy with Presenile Dementia. A recently discovered type of dementia, familial multiple system taupathy, shares some brain abnormalities found in people with Alzheimer's disease. The gene that causes the disorder is thought to be carried on chromosome 17. The symptoms of the disorder include short-term memory problems and difficulty maintaining balance and walking. The onset of disease occurs in the 40s and 50s, and persons with the disease live an average of 11 years after the onset of symptoms. As in patients with Alzheimer's disease, tau protein builds up in neurons and glial cells of persons with familial multiple system taupathy. Eventually, the protein buildup kills brain cells. The disorder is not associated with the senile plaques seen with Alzheimer's disease. Mr. J, a 70-year-old retired businessman, was brought to psychiatric services on referral by the family physician. His wife claimed that Mr. J had become so forgetful that she was afraid to leave him alone, even at home. Mr. J retired at age 62 years after experiencing a decline in work performance during the previous 5 years. He also slowly gave up hobbies he once enjoyed (photography, reading, golf) and became increasingly quiet. However, his growing forgetfulness went basically unnoticed at home. Then one day while walking in an area he knew well, he could not find his way home. From then on his memory failure began to increase. He would forget appointments, misplace things, and lose his way around the neighborhood he resided in for 40 years. He failed to recognize people, even those he knew for many years. His wife had to start bathing and dressing him because he forgot how to do so himself. On examination, Mr. J was disoriented in time and place. He was only able to recall his name and place of birth. Mr. J seemed lost during the interview, only responding to questions with an occasional shrug of his shoulders. When asked to name objects or to recall words or numbers, Mr. J appeared tense and distressed. Mr. J had

difficulty following instructions and was unable to dress or undress himself. His general medical condition was good. Laboratory examinations showed abnormalities on Mr. J's EEG and CT scans. Vascular Dementia The primary cause of vascular dementia, formerly referred to as multi-infarct dementia, is presumed to be multiple areas of cerebral vascular disease, resulting in a symptom pattern of dementia. Vascular dementia most commonly is seen in men, especially those with preexisting hypertension or other cardiovascular risk factors. The disorder affects primarily small- and medium-sized cerebral vessels, which undergo infarction and produce multiple parenchymal lesions spread over wide areas of the brain (Fig. 21.3-3).

The causes of the infarctions can include occlusion of the vessels by arteriosclerotic plaques or thromobemboli from distant origins (e.g., heart valves). An examination of a patient may reveal carotid bruits, funduscopic abnormalities, or enlarged cardiac chambers (Fig. 21.3-4). FIGURE 21.3-4 Patients with chronic dementia usually requires custodial care in their declining years. Regressive behavior, such as finger sucking, is typical in this state. (Courtesy of Bill Stanton for Magnum Photos, Inc.) FIGURE 21.3-3 Gross appearance of the cerebral cortex on coronal section from a patient with vascular dementia. The multiple bilateral lacunar infarcts involve the thalamus, the internal capsule, and the globus pallidus. (Courtesy of Daniel P. Perl, M.D.) Binswanger's Disease. Binswanger's disease (Fig. 21.3-5), also known as

subcortical arteriosclerotic encephalopathy, is characterized by the presence of many small infarctions of the white matter that spare the cortical regions (Fig. 21.3-6). Although Binswanger's disease was previously considered a rare condition, the advent of sophisticated and powerful imaging techniques, such as MRI, has revealed that the condition is more common than previously thought. FIGURE 21.3-5 Otto Binswanger (1852–1929), a Swiss psychiatrist who described a condition he call "encephalitis subcorticalis chronica progressive," now known as Binswanger's disease. FIGURE 21.3-6

Binswanger's disease. Cross-section demonstrating extensive subcortical white matter infarction, with sparing of the overlying gray matter. (Courtesy of Dushyant Purohit, M.D., Neuropathology Division, Mount Sinai School of Medicine, New York, NY.) Frontotemporal Dementia (Pick's Disease) In contrast to the parietal-temporal distribution of pathological findings in Alzheimer's disease, Pick's disease (Fig. 21.3-7) is characterized by a preponderance of atrophy in the frontotemporal regions. These regions also have neuronal loss; gliosis; and neuronal Pick's bodies, which are masses of cytoskeletal elements. Pick's bodies are seen in some postmortem specimens but are not necessary for the diagnosis. The cause of Pick's disease is unknown, but the disease constitutes approximately 5 percent of all irreversible dementias. It is most common in men, especially those who have a firstdegree relative with the condition. Pick's disease is difficult to distinguish from dementia of the Alzheimer's type, although the early stages of Pick's disease are more often characterized by personality and behavioral changes, with relative preservation of other cognitive functions, and it typically begins before 75 years of age. Familial cases may have an earlier onset, and some studies have shown that approximately half of the cases of Pick's disease are familial (Fig. 21.3-8). Features of Klüver-Bucy syndrome (e.g., hypersexuality, placidity, and hyperorality) are much more common in Pick's disease than in Alzheimer's disease. FIGURE 21.3-7 Arnold Pick (1851–1924), a Czech neurologist and psychiatrist who described frontotemporal dementia and the Pick bodies that are characteristic of the disorder.

FIGURE 21.3-8 Pick’s disease gross pathology. This demonstrates the marked frontal and temporal atrophy seen in frontotemporal dementias, such as Pick’s disease. (Courtesy of Dushyant Purohit, M.D., Neuropathology Division, Mount Sinai School of Medicine, New York, NY.) Lewy Body Disease Lewy body disease is a dementia clinically similar to Alzheimer’s disease and often characterized by hallucinations, parkinsonian features, and extrapyramidal signs (Table 21.3-2). Lewy inclusion bodies are found in the cerebral cortex (Fig. 21.3-9). The exact incidence is unknown. These patients often have Capgras syndrome (reduplicative paramnesia) as party of the clinical picture. FIGURE 21.3-9 Photomicrographs of Lewy body pathology. (A) Abnormal accumulation of α-synuclein aggregates demonstrated by immunocytochemistry in the amygdala of a subject with dementia. Lewy bodies appear as dense intracellular inclusions (arrows), but staining of neuronal processes can be seen throughout the neuropil (arrowheads). In individuals in whom Lewy body pathology occurs concurrently with Alzheimer’s disease, the amygdala is often the only region affected. (B) Classic appearance of a Lewy body (arrow) in a large pigmented neuron of the substantia nigra. (C) Lewy body pathology in the neocortex. Both Lewy bodies (arrows) and substantial labeling of neuronal processes in

the neuropil (arrowheads) are evident. (Magnification for [A] and [B] 200×, for [C] 400×. All images provided courtesy of Dr. Ronald L. Hamilton, Department of Pathology, Division of Neuropathology, University of Pittsburgh School of Medicine.) Table 21.3-2 Clinical Criteria for Dementia with Lewy Bodies (DLB) Huntington’s Disease Huntington’s disease (Fig. 21.3-10) is classically associated with the development of dementia. The dementia seen in this disease is the subcortical type of dementia, characterized by more motor abnormalities and fewer language abnormalities than in the cortical type of dementia (Table 21.3-3). The dementia of Huntington’s disease exhibits psychomotor slowing and difficulty with complex tasks, but memory, language, and insight remain relatively intact in the early and middle stages of the illness. As the disease progresses, however, the dementia becomes complete; the features distinguishing it from dementia of the Alzheimer’s type are the high incidence of depression and psychosis in addition to the classic choreoathetoid movement disorder.

FIGURE 21.3-10 George Huntington (1850–1916), an American physician who first described the disease that bears his name, Huntington’s disease. Table 21.3-3 Distinguishing Features of Subcortical and Cortical Dementias

Parkinson’s Disease As with Huntington’s disease, parkinsonism is a disease of the basal ganglia, commonly associated with dementia and depression. An estimated 20 to 30 percent of patients with Parkinson’s disease have dementia, and an additional 30 to 40 percent have measurable impairment in cognitive abilities. The slow movements of persons with Parkinson’s disease are paralleled in the slow thinking of some affected patients, a feature that clinicians may refer to as bradyphrenia. Mr. M, 77 years of age, came for a neurological examination because he noticed his memory was slipping and he was having difficulty concentrating, which interfered with his work. He complained of slowness and losing his train of thought. His wife stated that he was becoming withdrawn and was more reluctant to participate in activities he usually enjoyed. He denied symptoms of depression other than feeling mildly depressed about his disabilities. Two years prior, Mr. M developed an intermittent resting tremor in his right hand and a shuffling gait. Although a psychiatrist considered a diagnosis of Parkinson’s disease, it was not confirmed by a neurologist and therefore was never treated. During an initial neurological examination, Mr. M’s spontaneous

speech was hesitant and unclear (dysarthric). Cranial nerve examination was normal. Motor tone was increased slightly in the neck and all limbs. He performed alternating movements in his hands slowly. He had a slight intermittent tremor of his right arm at rest.

Reflexes were symmetrical. A neuropsychological examination was performed three weeks later. It was found that Mr. M showed impairment of memory, naming, and constructional abilities. HIV-Related Dementia Encephalopathy in HIV infection is associated with dementia and is termed acquired immune deficiency syndrome (AIDS) dementia complex, or HIV dementia. Patients infected with HIV experience dementia at an annual rate of approximately 14 percent. An estimated 75 percent of patients with AIDS have involvement of the CNS at the time of autopsy. The development of dementia in people infected with HIV is often paralleled by the appearance of parenchymal abnormalities in MRI scans. Other infectious dementias are caused by Cryptococcus or Treponema pallidum. The diagnosis of AIDS dementia complex is made by confirmation of HIV infection and exclusion of alternative pathology to explain cognitive impairment. The American Academy of Neurology AIDS Task Force developed research criteria for the clinical diagnosis of CNS disorders in adults and adolescents (Table 21.3-4). The AIDS Task Force criteria for AIDS dementia complex require laboratory evidence for systemic HIV, at least two cognitive deficits, and the presence of motor abnormalities or personality changes. Personality changes may be manifested by apathy, emotional lability, or behavioral disinhibition. The AIDS Task Force criteria also require the absence of clouding of consciousness or evidence of another etiology that could produce the cognitive impairment. Cognitive, motor, and behavioral changes are assessed using physical, neurological, and psychiatric examinations, in addition to neuropsychological testing. Table 21.3-4 Criteria for Clinical Diagnosis of HIV Type 1-Associated Dementia Complex

Head Trauma-Related Dementia Dementia can be a sequela of head trauma. The so-called punch-drunk syndrome (dementia pugilistica) occurs in boxers after repeated head trauma over many years. It is characterized by emotional lability, dysarthria, and impulsivity. It has also been observed in professional football players who developed dementia after repeated concussions over many years. Mrs. S, 75 years of age, was brought to the emergency department after being found wandering her neighborhood in a confused and disoriented state. She was in good health until a few months prior when her husband was hospitalized for 10 days for minor surgery. About a month after her husband returned home, he and their two adult children, who do not reside with them, reported a noticeable change in Mrs. S's mental status. Mrs. S became hyperactive and appeared to have excessive energy, was agitated and irritable, and had difficulty sleeping at night. At examination, Mrs. S was disoriented to time and place, agitated, and confused. Her husband revealed upon interview that Mrs. S has for many years suffered from dizziness and lightheadedness upon standing and occasionally suffered from falls, none of which caused any major damage. Not long before her confused symptoms began, Mrs. S had apparently suffered a fall one night, and her husband found her the next morning lying next to the bed in a confused state. Because of her history of falls,

neither Mr. S nor Mrs. S thought much of the incident. A CT scan revealed the presence of a subdural hematoma, which was then evacuated. Afterward, Mrs. S's confusion and disorientation cleared and she returned to her normal state of functioning. DIAGNOSIS AND CLINICAL FEATURES The DSM-5 diagnostic criteria are listed in Tables 21.3-5 and 21.3-6. DSM-5 makes a distinction between major and minor cognitive disorder based upon levels of functioning, but the underlying

etiology is similar. Table 21.3-5 DSM-5 Diagnostic Criteria for Major Neurocognitive Disorder (Dementia) Table 21.3-6 DSM-5 Diagnostic Criteria for Major or Mild Neurocognitive Disorder Due to Alzheimer’s Disease

The diagnosis of dementia is based on the clinical examination, including a mental status examination, and on information from the patient’s family, friends, and employers. Complaints of a personality change in a patient older than age 40 years suggest that a diagnosis of dementia should be carefully considered. Clinicians should note patients’ complaints about intellectual impairment and forgetfulness as well as evidence of patients’ evasion, denial, or rationalization aimed at concealing cognitive deficits. Excessive orderliness, social withdrawal, or a tendency to relate events in minute detail can be characteristic, and sudden outbursts of anger or sarcasm can occur. Patients’ appearance and behavior should be observed. Lability of emotions; sloppy grooming; uninhibited remarks; silly jokes; or a dull, apathetic, or vacuous facial expression and manner suggest the presence of dementia, especially when coupled with memory impairment. Memory impairment is typically an early and prominent feature in dementia, especially in dementias involving the cortex, such as dementia of the Alzheimer’s type. Early in the course of dementia, memory impairment is mild and usually most marked for recent events; people forget telephone numbers, conversations, and events of the day. As the course of dementia progresses, memory impairment becomes severe, and only the earliest learned information (e.g., a person’s place of birth) is retained. Inasmuch as memory is important for orientation to person, place, and time, orientation can be progressively affected during the course of a dementing illness. For

example, patients with dementia may forget how to get back to their rooms after going to the bathroom. No matter how severe the disorientation seems, however, patients show no impairment in their level of consciousness. Dementing processes that affect the cortex, primarily dementia of the Alzheimer’s type and vascular dementia, can affect patients’ language abilities. Psychiatric and Neurological Changes Personality. Changes in the personality of a person with dementia are especially disturbing for their families. Preexisting personality traits may be accentuated during the development of a dementia. Patients with dementia may also become introverted and seem to be less concerned than they previously were about the effects of their behavior on others. Persons with dementia who have paranoid delusions are generally hostile to family members and caretakers. Patients with frontal and temporal involvement are likely to have marked personality changes and may be irritable and explosive. Hallucinations and Delusions. An estimated 20 to 30 percent of patients with dementia (primarily patients with dementia of the Alzheimer’s type) have hallucinations, and 30 to 40 percent have delusions, primarily of a paranoid or persecutory and unsystematized nature, although complex, sustained, and wellsystematized delusions are also reported by these patients. Physical aggression and other forms of violence are common in demented patients who also have psychotic symptoms. Mood. In addition to psychosis and personality changes, depression and anxiety are major symptoms in an estimated 40 to 50 percent of patients with dementia, although the full syndrome of depressive disorder may be present in only 10 to 20 percent. Patients with dementia also may exhibit pathological laughter or crying—that is, extremes of emotions—with no apparent provocation. Cognitive Change. In addition to the aphasias in patients with dementia, apraxias and agnosias are common. Other neurological signs that can be associated with dementia are seizures, seen in approximately 10 percent of patients with dementia of the Alzheimer’s type and in 20 percent of patients with vascular dementia, and atypical neurological presentations, such as nondominant parietal lobe syndromes.

Primitive reflexes, such as the grasp, snout, suck, tonic-foot, and palmomental reflexes, may be present on neurological examination, and myoclonic jerks are present in 5 to 10 percent of patients. Patients with vascular dementia may have additional neurological symptoms, such as headaches, dizziness, faintness, weakness, focal neurological signs, and sleep disturbances, possibly attributable to the location of the cerebrovascular disease. Pseudobulbar palsy, dysarthria, and dysphagia are also more common in vascular

dementia than in other dementing conditions. Catastrophic Reaction. Patients with dementia also exhibit a reduced ability to apply what Kurt Goldstein called the “abstract attitude.” Patients have difficulty generalizing from a single instance, forming concepts, and grasping similarities and differences among concepts. Furthermore, the ability to solve problems, to reason logically, and to make sound judgments is compromised. Goldstein also described a catastrophic reaction marked by agitation secondary to the subjective awareness of intellectual deficits under stressful circumstances. Persons usually attempt to compensate for defects by using strategies to avoid demonstrating failures in intellectual performance; they may change the subject, make jokes, or otherwise divert the interviewer. Lack of judgment and poor impulse control appear commonly, particularly in dementias that primarily affect the frontal lobes. Examples of these impairments include coarse language, inappropriate jokes, neglect of personal appearance and hygiene, and a general disregard for the conventional rules of social conduct. Sundowner Syndrome. Sundowner syndrome is characterized by drowsiness, confusion, ataxia, and accidental falls. It occurs in older people who are overly sedated and in patients with dementia who react adversely to even a small dose of a psychoactive drug. The syndrome also occurs in demented patients when external stimuli, such as light and interpersonal orienting cues, are diminished. Vascular Dementia The general symptoms of vascular dementia are the same as those for dementia of the Alzheimer’s type, but the diagnosis of vascular dementia requires either clinical or laboratory evidence in support of a vascular cause of the dementia. Vascular dementia is more likely to show a decremental, stepwise deterioration than is Alzheimer’s disease. Substance-Induced Persisting Dementia To facilitate the clinician’s thinking about differential diagnosis, substance-induced persisting dementia is listed in two places, with the dementias and with the substancerelated disorders. The specific substances that cross references are alcohol, inhalants, sedatives, hypnotics, or anxiolytics, and other or unknown substances. Alcohol-Induced Persisting Dementia. To make the diagnosis of alcoholinduced persisting dementia, the criteria for dementia must be met. Because amnesia can also occur in the context of Korsakoff’s psychosis, it is important to distinguish between memory impairment accompanied by other cognitive deficits (i.e., dementia) and amnesia caused by thiamine deficiency. To complicate matters, however, evidence also suggests that other cognitive functions, such as attention and concentration, may also be impaired in Wernicke-Korsakoff syndrome. In addition, alcohol abuse is frequently associated with mood changes, so poor concentration and other cognitive

symptoms often observed in the context of a major depression must also be ruled out. Prevalence rates differ considerably according to the population studied and the diagnostic criteria used, although alcohol-related dementia has been estimated to account for approximately 4 percent of dementias. PATHOLOGY, PHYSICAL FINDINGS, AND LABORATORY EXAMINATION A comprehensive laboratory workup must be performed when evaluating a patient with dementia. The purposes of the workup are to detect reversible causes of dementia and to provide the patient and family with a definitive diagnosis. The range of possible causes of dementia mandates selective use of

laboratory tests. The evaluation should follow informed clinical suspicion based on the history and physical and mental status examination results. The continued improvements in brain imaging techniques, particularly MRI, have made differentiation between dementia of the Alzheimer's type and vascular dementia, in some cases, somewhat more straightforward than in the past. An active area of research is the use of single-photon emission computed tomography (SPECT) to detect patterns of brain metabolism in various types of dementias; the use of SPECT images may soon help in the clinical differential diagnosis of dementing illnesses. A general physical examination is a routine component of the workup for dementia. It may reveal evidence of systemic disease causing brain dysfunction, such as an enlarged liver and hepatic encephalopathy, or it may demonstrate systemic disease related to particular CNS processes. The detection of Kaposi's sarcoma, for example, should alert the clinician to the probable presence of AIDS and the associated possibility of AIDS dementia complex. Focal neurological findings, such as asymmetrical hyperreflexia or weakness, are seen more often in vascular than in degenerative disease. Frontal lobe signs and primitive reflexes occur in many disorders and often point to greater progression. DIFFERENTIAL DIAGNOSIS Dementia of the Alzheimer's Type versus Vascular Dementia Classically, vascular dementia has been distinguished from dementia of the Alzheimer's type by the decremental deterioration that can accompany cerebrovascular disease over time. Although the discrete, stepwise deterioration may not be apparent in all cases, focal neurological symptoms are more common in vascular dementia than in dementia of the Alzheimer's type, as are the standard risk factors for cerebrovascular disease. Vascular Dementia versus Transient Ischemic Attacks Transient ischemic attacks (TIAs) are brief episodes of focal neurological dysfunction lasting less than 24 hours (usually 5 to 15 minutes). Although a variety of mechanisms may be responsible, the episodes are frequently the result of microembolization from a

proximal intracranial arterial lesion that produces transient brain ischemia, and the episodes usually resolve without significant pathological alteration of the parenchymal tissue. Approximately one-third of persons with untreated TIAs experience a brain infarction later; therefore, recognition of TIAs is an important clinical strategy to prevent brain infarction. Clinicians should distinguish episodes involving the vertebrobasilar system from those involving the carotid arterial system. In general, symptoms of vertebrobasilar disease reflect a transient functional disturbance in either the brainstem or the occipital lobe; carotid distribution symptoms reflect unilateral retinal or hemispheric abnormality. Anticoagulant therapy, antiplatelet agglutinating drugs such as aspirin, and extracranial and intracranial reconstructive vascular surgery are effective in reducing the risk of infarction in patients with TIAs. Delirium In general, delirium is distinguished by rapid onset, brief duration, cognitive impairment fluctuation during the course of the day; nocturnal exacerbation of symptoms; marked disturbance of the sleep–wake cycle; and prominent disturbances in attention and perception. Depression Some patients with depression have symptoms of cognitive impairment difficult to distinguish from symptoms of dementia. The clinical picture is sometimes referred to as pseudodementia, although the term depression-related cognitive dysfunction is preferable and more descriptive (Table 21.3-7). Patients with depression-related cognitive dysfunction generally have prominent depressive symptoms, more insight into their symptoms than do demented patients, and often a history of depressive episodes. Table 21.3-7 Major Clinical Features Differentiating Pseudodementia from Dementia

Factitious Disorder Persons who attempt to simulate memory loss, as in factitious disorder, do so in an erratic and inconsistent manner. In true dementia, memory for time and place is lost before

memory for person, and recent memory is lost before remote memory. Schizophrenia Although schizophrenia can be associated with some acquired intellectual impairment, its symptoms are much less severe than are the related symptoms of psychosis and thought disorder seen in dementia. Normal Aging Aging is not necessarily associated with any significant cognitive decline, but minor memory problems can occur as a normal part of aging. These normal occurrences are sometimes referred to as benign senescent forgetfulness, age-associated memory impairment, or normal benign age-related senescence. They are distinguished from dementia by their minor severity and because they do not interfere significantly with a person's social or occupational behavior. See Section 21.6 for a discussion of mild cognitive impairment. Other Disorders

Intellectual disability, which does not include memory impairment, occurs in childhood. Amnestic disorder is characterized by circumscribed loss of memory and no deterioration. Major depression in which memory is impaired responds to antidepressant medication. Malingering and pituitary disorder must be ruled out, but they are unlikely. COURSE AND PROGNOSIS The classic course of dementia is an onset in the patient's 50s or 60s, with gradual deterioration over 5 to 10 years, leading eventually to death. The age of onset and the rapidity of deterioration vary among different types of dementia and within individual diagnostic categories. The average survival expectation for patients with dementia of the Alzheimer's type is approximately 8 years, with a range of 1 to 20 years. Data suggest that in persons with an early onset of dementia or with a family history of dementia, the disease is likely to have a rapid course. In a recent study of 821 persons with Alzheimer's disease, the median survival time was 3.5 years. After dementia is diagnosed, patients must have a complete medical and neurological workup because 10 to 15 percent of all patients with dementia have a potentially reversible condition if treatment is initiated before permanent brain damage occurs. The most common course of dementia begins with a number of subtle signs that may, at first, be ignored by both the patient and the people closest to the patient. A gradual onset of symptoms is most commonly associated with dementia of the Alzheimer's type, vascular dementia, endocrinopathies, brain tumors, and metabolic disorders. Conversely, the onset of dementia resulting from head trauma, cardiac arrest with cerebral hypoxia, or encephalitis can be sudden. Although the symptoms of the early phase of dementia are subtle, they become conspicuous as the dementia progresses, and family members may then bring a patient to a physician's attention. People with dementia may be sensitive to the use of benzodiazepines or alcohol, which can precipitate agitated, aggressive, or psychotic behavior. In the terminal stages of dementia, patients become empty shells of their former selves—profoundly disoriented, incoherent, amnestic, and incontinent of urine and feces. With psychosocial and pharmacological treatment and possibly because of the selfhealing properties of the brain, the symptoms of dementia may progress slowly for a time or may even recede somewhat. Symptom regression is certainly a possibility in reversible dementias (dementias caused by hypothyroidism, NPH, and brain tumors) after treatment is initiated. The course of the dementia varies from a steady progression (commonly seen with dementia of the Alzheimer's type) to an incrementally worsening dementia (commonly seen with vascular dementia) to a stable dementia (as may be seen in dementia related to head trauma). Psychosocial Determinants The severity and course of dementia can be affected by psychosocial factors. The greater a person's premorbid intelligence and education, the better the ability to compensate for

intellectual deficits. People who have a rapid onset of dementia use fewer defenses than do those who experience an insidious onset. Anxiety and depression can intensify and aggravate the

symptoms. Pseudodementia occurs in depressed people who complain of impaired memory but, in fact, have a depressive disorder. When the depression is treated, the cognitive defects disappear. TREATMENT The first step in the treatment of dementia is verification of the diagnosis. Accurate diagnosis is imperative because the progression may be halted or even reversed if appropriate therapy is provided. Preventive measures are important, particularly in vascular dementia. Such measures might include changes in diet, exercise, and control of diabetes and hypertension. Pharmacological agents might include antihypertensive, anticoagulant, or antiplatelet agents. Blood pressure control should aim for the higher end of the normal range because that has been demonstrated to improve cognitive function in patients with vascular dementia. Blood pressure below the normal range has been demonstrated to further impair cognitive function in patients with dementia. The choice of antihypertensive agent can be significant in that β-adrenergic receptor antagonists have been associated with exaggeration of cognitive impairment. Angiotensin-converting enzyme (ACE) inhibitors and diuretics have not been linked to exaggeration of cognitive impairment and are thought to lower blood pressure without affecting cerebral blood flow, which is presumed to be correlated with cognitive function. Surgical removal of carotid plaques may prevent subsequent vascular events in carefully selected patients. The general treatment approach to patients with dementia is to provide supportive medical care; emotional support for the patients and their families; and pharmacological treatment for specific symptoms, including disruptive behavior. Psychosocial Therapies The deterioration of mental faculties has significant psychological meaning for patients with dementia. The experience of a sense of continuity over time depends on memory. Recent memory is lost before remote memory in most cases of dementia, and many patients are highly distressed by clearly recalling how they used to function while observing their obvious deterioration. At the most fundamental level, the self is a product of brain functioning. Patients' identities begin to fade as the illness progresses, and they can recall less and less of their past. Emotional reactions ranging from depression to severe anxiety to catastrophic terror can stem from the realization that the sense of self is disappearing. Patients often benefit from a supportive and educational psychotherapy in which the nature and course of their illness are clearly explained. They may also benefit from assistance in grieving and accepting the extent of their disability and from attention to self-esteem issues. Any areas of intact functioning should be maximized by helping patients identify activities in which successful functioning is possible. A psychodynamic

assessment of defective ego functions and cognitive limitations can also be useful. Clinicians can help patients find ways to deal with the defective ego functions, such as keeping calendars for orientation problems, making schedules to help structure activities, and taking notes for memory problems. Psychodynamic interventions with family members of patients with dementia may be of great assistance. Those who take care of a patient struggle with feelings of guilt, grief, anger, and exhaustion as they watch a family member gradually deteriorate. A common problem that develops among caregivers involves their self-sacrifice in caring for a patient. The gradually developing resentment from this self-sacrifice is often suppressed because of the guilt feelings it produces. Clinicians can help caregivers understand the complex mixture of feelings associated with seeing a loved one decline and can provide understanding as well as permission to express these feelings. Clinicians must also be aware of the caregivers' tendencies to blame themselves or others for patients' illnesses and must appreciate the role that patients with dementia play in the lives of family members. Pharmacotherapy Clinicians may prescribe benzodiazepines for insomnia and anxiety, antidepressants for depression, and antipsychotic drugs for delusions and

hallucinations, but they should be aware of possible idiosyncratic drug effects in older people (e.g., paradoxical excitement, confusion, and increased sedation). In general, drugs with high anticholinergic activity should be avoided. Donepezil (Aricept), rivastigmine (Exelon), galantamine (Remiryl), and tacrine (Cognex) are cholinesterase inhibitors used to treat mild to moderate cognitive impairment in Alzheimer's disease. They reduce the inactivation of the neurotransmitter acetylcholine and thus potentiate the cholinergic neurotransmitter, which in turn produces a modest improvement in memory and goal-directed thought. These drugs are most useful for persons with mild to moderate memory loss who have sufficient preservation of their basal forebrain cholinergic neurons to benefit from augmentation of cholinergic neurotransmission. Donepezil is well tolerated and widely used. Tacrine is rarely used because of its potential for hepatotoxicity. Fewer clinical data are available for rivastigmine and galantamine, which appear more likely to cause gastrointestinal (GI) and neuropsychiatric adverse effects than does donepezil. None of these medications prevents the progressive neuronal degeneration of the disorder. Prescribing information for anticholinesterase inhibitors can be found in Section 36.14. Memantine (Namenda) protects neurons from excessive amounts of glutamate, which may be neurotoxic. The drug is sometimes combined with donepezil. It has been known to improve dementia. Other Treatment Approaches. Other drugs being tested for cognitive-enhancing activity include general cerebral metabolic enhancers, calcium channel inhibitors, and

serotonergic agents. Some studies have shown that selegiline (Eldepryl), a selective type B monoamine oxidase (MAOB) inhibitor, may slow the advance of this disease. Ondansetron (Zofran), a 5-HT3 receptor antagonist, is under investigation. Estrogen replacement therapy may reduce the risk of cognitive decline in postmenopausal women; however, more studies are needed to confirm this effect. Complementary and alternative medicine studies of ginkgo biloba and other phytomedicinals are required to see if they have a positive effect on cognition. Reports have appeared of patients using nonsteroidal antiinflammatory agents having a lower risk of developing Alzheimer's disease. Vitamin E has not been shown to be of value in preventing the disease. REFERENCES Bondi MW, Salmon DP, Kaszniak AW. The neuropsychology of dementia. In: Grant I, Adams KM, eds. Neuropsychological Assessment of Neuropsychiatric and Neuromedical Disorders. 3rd ed. New York: Oxford University Press; 2009:159. Brand BL, Stadnik R. What contributes to predicting change in the treatment of dissociation: Initial levels of dissociation, PTSD, or overall distress? J Trauma Dissociation. 2013;14:328. Clare L, Whitaker CJ, Nelis SM, et al. Self-concept in early stage dementia: Profile, course, correlates, predictors and implications for quality of life. Int J Geriatr Psychiatry. 2013;28(5):494–503. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia. Arch Neurol. 2009;66(3):300. Elvish R, Lever S-J, Johnstone J, Cawley R, Keady J. Psychological interventions for carers of people with dementia: A systematic review of quantitative and qualitative evidence. Counsel Psychother Res. 2013;13(2):106–125. Goldman J, Stebbins G, Merkitch D, Dinh V, Bernard B, DeToledo-Morrell L, Goetz C. Hallucinations and dementia in Parkinson's disease: clinically related but structurally distinct (P5. 257). Neurology. 2014;82(10 Supplement):P5-257. Graff-Radford NR, Woodruff BK. Frontotemporal dementia. Semin Neurol. 2007; 27:48. Hansen KF, Karenlina K, Sakamoto K, Wayman GA, Impey S, Obrietan K. miRNA-132: A dynamic regulator of cognitive capacity. Brain Structure Function. 2013;218:817. Insausti R, Annese J, Amaral DG, Squire LR. Human amnesia and the medial temporal lobe illuminated by neuropsychological and neurohistological findings for patient E.P. Proc Natl Acad Sci U S A. 2013;110:E1953. Kemp PM, Holmes C. Imaging in dementia with Lewy bodies: A review. Nucl Med Commun. 2007;28:511. McLaren AN, LaMantia MA, Callahan CM. Systematic review of non-

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04 - 21.4 Major or Minor Neurocognitive Disorder D

21.4 Major or Minor Neurocognitive Disorder Due to Another Medical Condition (Amnestic Disorders)

Watson PD, Voss JL, Warren DE, Tranel D, Cohen NJ. Spatial reconstruction by patients with hippocampal damage is dominated by relational memory errors. Hippocampus. 2013;23:570. 21.4 Major or Minor Neurocognitive Disorder Due to Another Medical Condition (Amnestic Disorders) The amnestic disorders are coded in the DSM-5 as “major or minor neurocognitive disorders due to another medical condition.” All of these disorders cause impairment in memory as the major sign and symptom, although other signs of cognitive decline may coexist. The authors of Synopsis believe amnestic disorder to be a clinically useful descriptive category of illness, but they are coded in DSM-5 as a neurocognitive disorder due to another medical condition with the specific medical condition noted. The amnestic disorders are a broad category that results from a variety of diseases and conditions that have amnesia as the major complaint. The syndrome is defined primarily by impairment in the ability to create new memories. Three different etiologies exist: amnestic disorder caused by a general medical condition (e.g., head trauma), substance-induced persisting amnestic disorder (e.g., caused by carbon monoxide poisoning or chronic alcohol consumption), and amnestic disorder not otherwise specified for cases in which the etiology is unclear. EPIDEMIOLOGY No adequate studies have reported on the incidence or prevalence of amnestic disorders. Amnesia is most commonly found in alcohol use disorders and in head injury. In general practice and hospital settings, the frequency of amnesia related to chronic alcohol abuse has decreased, and the frequency of amnesia related to head trauma has increased. ETIOLOGY The major neuroanatomical structures involved in memory and in the development of an amnestic disorder are particular diencephalic structures such as the dorsomedial and midline nuclei of the thalamus and midtemporal lobe structures such as the hippocampus, the mamillary bodies, and the amygdala. Although amnesia is usually the result of bilateral damage to these structures, some

cases of unilateral damage result in an amnestic disorder, and evidence indicates that the left hemisphere may be more critical than the right hemisphere in the development of memory disorders. Many studies of memory and amnesia in animals have suggested that other brain areas may also be involved in the symptoms accompanying amnesia. Frontal lobe involvement can result in such symptoms as confabulation and apathy, which can be seen in patients with amnestic disorders. Amnestic disorders have many potential causes (Table 21.4-1). Thiamine deficiency, hypoglycemia, hypoxia (including carbon monoxide poisoning), and herpes simplex encephalitis all have a predilection to damage the temporal lobes, particularly the

hippocampi, and thus can be associated with the development of amnestic disorders. Similarly, when tumors, cerebrovascular diseases, surgical procedures, or multiple sclerosis plaques involve the diencephalic or temporal regions of the brain, the symptoms of an amnestic disorder may develop. General insults to the brain, such as seizures, ECT, and head trauma, can also result in memory impairment. Transient global amnesia is presumed to be a cerebrovascular disorder involving transient impairment in blood flow through the vertebrobasilar arteries. Table 21.4-1 Major Causes of Amnestic Disorders Many drugs have been associated with the development of amnesia, and clinicians should review all drugs taken, including nonprescription drugs, in the diagnostic workup of a patient with amnesia. The benzodiazepines are the most commonly used prescription drugs associated with amnesia. All benzodiazepines can be associated with amnesia, especially if combined with alcohol. When triazolam (Halcion) is used in doses of 0.25 mg or less, which are generally equivalent to standard doses of other benzodiazepines, amnesia is no more often associated with triazolam than with other benzodiazepines. With alcohol and higher doses, anterograde amnesia has been reported. DIAGNOSIS The recognition of amnestic disorder occurs when impairment in the ability to learn new information or the inability to recall previously learned information, as a result of which there is significant impairment in social or occupational functioning and which is caused by a general medical condition (including physical trauma). Amnestic disorder may be transient, lasting for hours or days or chronic lasting weeks or months. A diagnosis of substance-induced persisting amnestic disorder is made when evidence

suggests that the symptoms are causatively related to the use of a substance. The DSM-5 refers clinicians to specific diagnoses within substance-related disorders: alcohol-induced disorder; sedative, hypnotic, or anxiolytic-induced disorder; and other (or unknown) substance-induced disorder. CLINICAL FEATURES AND SUBTYPES The central symptom of amnestic disorders is the development of a memory disorder characterized by an impairment in the ability to learn new information (anterograde amnesia) and an inability to recall previously remembered knowledge (retrograde amnesia). The symptom must result in significant problems for patients in their social or occupational functioning. The time in which a patient is amnestic can begin directly at the point of trauma or include a period before the trauma. Memory for the time during the physical insult (e.g., during a cerebrovascular event) may also be lost. Short-term and recent memory are usually impaired. Patients cannot remember what they had for breakfast or lunch, the name of the hospital, or their doctors. In some patients, the amnesia is so profound that the patient cannot orient himself or herself to city and time, although orientation to person is seldom lost in amnestic disorders. Memory for overlearned information or events from the remote past, such as childhood experiences, is good, but memory for events from the less remote past (over the past decade) is impaired. Immediate memory (tested, for example, by asking a patient to repeat six numbers) remains intact. With improvement, patients may experience a gradual shrinking of the time for

which memory has been lost, although some patients experience a gradual improvement in memory for the entire period. The onset of symptoms can be sudden, as in trauma, cerebrovascular events, and neurotoxic chemical assaults, or gradual, as in nutritional deficiency and cerebral tumors. The amnesia can be of short duration. A variety of other symptoms can be associated with amnestic disorders. For patients with other cognitive impairments, a diagnosis of dementia or delirium is more appropriate than a diagnosis of an amnestic disorder. Both subtle and gross changes in personality can accompany the symptoms of memory impairment in amnestic disorders. Patients may be apathetic, lack initiative, have unprovoked episodes of agitation, or appear to be overly friendly or agreeable. Patients with amnestic disorders can also appear bewildered and confused and may attempt to cover their confusion with confabulatory answers to questions. Characteristically, patients with amnestic disorders do not have good insight into their neuropsychiatric conditions. A 73-year-old survivor of the Holocaust was admitted to the psychiatric unit from a local nursing home. She was born in Germany to a middle-class family. Her education was truncated because of internment in a concentration camp. She immigrated to Israel after liberation from the concentration camp and later to the United States, where she married and raised a family. Premorbidly, she was described as a quiet,

intelligent, and loving woman who spoke several languages. At 55 years of age, she had a significant carbon monoxide exposure when a gas line leaked while she and her husband slept. Her husband died of carbon monoxide poisoning, but the patient survived after a period of coma. After being stabilized, she displayed significant cognitive and behavioral problems. She had difficulty with learning new information and making appropriate plans. She retained the ability to perform activities of daily living but could not be relied on to pay bills, buy food, cook, or clean, despite appearing to have retained the intellectual ability to do these tasks. She was admitted to a nursing home after several difficult years at home and in the homes of relatives. In the nursing home, she was able to learn her way about the facility. She displayed little interest in scheduled group activities, hobbies, reading, or television. She had frequent behavioral problems. She repeatedly pressed staff to get her sweets and snacks and cursed them vociferously with racial epithets and disparaging comments on their weight and dress. On one occasion, she scratched the cars of several staff with a key. Neuropsychological testing demonstrated severe deficits in delayed recall; intact performance on language and general knowledge measures; and moderate deficits on domains of executive function, such as concept formation and cognitive flexibility. She was noted to respond immediately to firmly set limits and rewards, but deficits in memory prevented long-term incorporation of these boundaries. Management involved development of a behavioral plan that could be implemented at the nursing home and empirical trials of medications aimed at amelioration of irritability. Cerebrovascular Diseases Cerebrovascular diseases affecting the hippocampus involve the posterior cerebral and basilar arteries and their branches. Infarctions are rarely limited to the hippocampus; they often involve the occipital or parietal lobes. Thus, common accompanying symptoms of cerebrovascular diseases in this region are focal neurological signs involving vision or sensory modalities. Cerebrovascular diseases affecting the bilateral medial thalamus, particularly the anterior portions, are often associated with symptoms of amnestic disorders. A few case studies report amnestic disorders from rupture of an aneurysm of the anterior communicating artery, resulting in infarction of the basal forebrain region. Multiple Sclerosis The pathophysiological process of multiple sclerosis involves the seemingly random formation of plaques within the brain parenchyma. When the plaques occur in the temporal lobe and the diencephalic regions, symptoms of memory impairment can occur. In fact, the most

common cognitive complaints in patients with multiple sclerosis involve impaired memory, which occurs in 40 to 60 percent of patients. Characteristically, digit span memory is normal, but immediate recall and delayed recall

of information are impaired. The memory impairment can affect both verbal and nonverbal material. Korsakoff's Syndrome Korsakoff's syndrome is an amnestic syndrome caused by thiamine deficiency, most commonly associated with the poor nutritional habits of people with chronic alcohol abuse. Other causes of poor nutrition (e.g., starvation), gastric carcinoma, hemodialysis, hyperemesis gravidarum, prolonged IV hyperalimentation, and gastric plication can also result in thiamine deficiency. Korsakoff's syndrome is often associated with Wernicke's encephalopathy, which is the associated syndrome of confusion, ataxia, and ophthalmoplegia. In patients with these thiamine deficiency–related symptoms, the neuropathological findings include hyperplasia of the small blood vessels with occasional hemorrhages, hypertrophy of astrocytes, and subtle changes in neuronal axons. Although the delirium clears up within a month or so, the amnestic syndrome either accompanies or follows untreated Wernicke's encephalopathy in approximately 85 percent of all cases. Patients with Korsakoff's syndrome typically demonstrate a change in personality as well, such that they display a lack of initiative, diminished spontaneity, and a lack of interest or concern. These changes appear frontal lobe–like, similar to the personality change ascribed to patients with frontal lobe lesions or degeneration. Indeed, such patients often demonstrate executive function deficits on neuropsychological tasks involving attention, planning, set shifting, and inferential reasoning consistent with frontal pattern injuries. For this reason, Korsakoff's syndrome is not a pure memory disorder, although it certainly is a good paradigm of the more common clinical presentations for the amnestic syndrome. The onset of Korsakoff's syndrome can be gradual. Recent memory tends to be affected more than is remote memory, but this feature is variable. Confabulation, apathy, and passivity are often prominent symptoms in the syndrome. With treatment, patients may remain amnestic for up to 3 months and then gradually improve over the ensuing year. Administration of thiamine may prevent the development of additional amnestic symptoms, but the treatment seldom reverses severe amnestic symptoms when they are present. Approximately one-third to one-fourth of all patients recover completely, and approximately one-fourth of all patients have no improvement of their symptoms. Alcoholic Blackouts Some persons with severe alcohol abuse may exhibit the syndrome commonly referred to as an alcoholic blackout. Characteristically, these persons awake in the morning with a conscious awareness of being unable to remember a period the night before during which they were intoxicated. Sometimes specific behaviors (hiding money in a secret place and provoking fights) are associated with the blackouts.

Electroconvulsive Therapy Electroconvulsive therapy treatments are usually associated with retrograde amnesia for a period of several minutes before the treatment and anterograde amnesia after the treatment. The anterograde amnesia usually resolves within 5 hours. Mild memory deficits may remain for 1 to 2 months after a course of ECT treatments, but the symptoms are completely resolved 6 to 9 months after treatment. Head Injury Head injuries (both closed and penetrating) can result in a wide range of neuropsychiatric symptoms, including dementia, depression, personality changes, and amnestic disorders. Amnestic disorders caused by head injuries are commonly associated with a period of retrograde amnesia leading up to the traumatic incident and amnesia for the traumatic incident itself. The severity of the brain injury correlates somewhat with the duration and severity of the amnestic syndrome, but the best correlate of eventual

improvement is the degree of clinical improvement in the amnesia during the first week after the patient regains consciousness. Transient Global Amnesia Transient global amnesia is characterized by the abrupt loss of the ability to recall recent events or to remember new information. The syndrome is often characterized by mild confusion and a lack of insight into the problem; a clear sensorium; and, occasionally, the inability to perform some well-learned complex tasks. Episodes last from 6 to 24 hours. Studies suggest that transient global amnesia occurs in 5 to 10 cases per 100,000 persons per year, although, for patients older than age 50 years, the rate may be as high as 30 cases per 100,000 persons per year. The pathophysiology is unknown, but it likely involves ischemia of the temporal lobe and the diencephalic brain regions. Several studies of patients with SPECT have shown decreased blood flow in the temporal and parietotemporal regions, particularly in the left hemisphere. Patients with transient global amnesia almost universally experience complete improvement, although one study found that approximately 20 percent of patients may have recurrence of the episode, and another study found that approximately 7 percent of patients may have epilepsy. Patients with transient global amnesia have been differentiated from patients with transient ischemic attacks in that fewer patients have diabetes, hypercholesterolemia, and hypertriglyceridemia, but more have hypertension and migrainous episodes. PATHOLOGY AND LABORATORY EXAMINATION Laboratory findings diagnostic of amnestic disorder may be obtained using quantitative neuropsychological testing. Standardized tests also are available to assess recall of wellknown historical events or public figures to characterize an individual’s inability to

remember previously learned information. Performance on such tests varies among individuals with amnestic disorder. Subtle deficits in other cognitive functions may be noted in individuals with amnestic disorder. Memory deficits, however, constitute the predominant feature of the mental status examination and account largely for any functional deficits. No specific or diagnostic features are detectable on imaging studies such as MRI or CT. Damage of midtemporal lobe structures is common, however, and may be reflected in enlargement of third ventricle or temporal horns or in structural atrophy detected by MRI. DIFFERENTIAL DIAGNOSIS Table 21.4-1 lists the major causes of amnestic disorders. To make the diagnosis, clinicians must obtain a patient’s history, conduct a complete physical examination, and order all appropriate laboratory tests. Other diagnoses, however, can be confused with the amnestic disorders. Dementia and Delirium Amnestic disorders can be distinguished from delirium because they occur in the absence of a disturbance of consciousness and are striking for the relative preservation of other cognitive domains. Table 21.4-2 outlines the key distinctions between Alzheimer’s dementia and the amnestic disorders. Both disorders can have an insidious onset with slow progression, as in a Korsakoff’s psychosis in a chronic drinker. Amnestic disorders, however, can also develop precipitously, as in Wernicke’s encephalopathy, transient global amnesia, or anoxic insults. Although Alzheimer’s dementia progresses relentlessly, amnestic disorders tend to remain static or even improve after the offending cause has been removed. In terms of the actual memory deficits, the amnestic disorder and Alzheimer’s disease still differ. Alzheimer’s disease has an impact on retrieval in addition to encoding and consolidation. The deficits in Alzheimer’s disease extend beyond memory to general knowledge (semantic memory), language, praxis, and general function. These are spared in amnestic disorders. The dementias associated with Parkinson’s disease, AIDS, and other subcortical disorders demonstrate disproportionate impairment of retrieval, but relatively intact encoding and consolidation and thus can be distinguished from amnestic disorders. The subcortical pattern dementias are also likely to display motor symptoms, such as bradykinesia, chorea, or tremor, that are not components of the amnestic disorders. Table 21.4-2 Comparison of

Syndrome Characteristics in Alzheimer’s Disease and Amnestic Disorder

Normal Aging Some minor impairment in memory may accompany normal aging, but the requirement that the memory impairment cause significant impairment in social or occupational functioning should exclude normal aging from the diagnosis. Dissociative Disorders The dissociative disorders can sometimes be difficult to differentiate from the amnestic disorders. Patients with dissociative disorders, however, are more likely to have lost their orientation to self and may have more selective memory deficits than do patients with amnestic disorders. For example, patients with dissociative disorders may not know their names or home addresses, but they are still able to learn new information and remember selected past memories. Dissociative disorders are also often associated with emotionally stressful life events involving money, the legal system, or troubled relationships. Factitious Disorders Patients with factitious disorders who are mimicking an amnestic disorder often have inconsistent results on memory tests and have no evidence of an identifiable cause. These findings, coupled with evidence of primary or secondary gain for a patient, should suggest a factitious disorder. COURSE AND PROGNOSIS The course of an amnestic disorder depends on its etiology and treatment, particularly acute treatment. Generally, the amnestic disorder has a static course. Little improvement is seen over time, but also no progression of the disorder occurs. The exceptions are the acute amnesias, such as transient global amnesia, which resolves entirely over hours to days, and the amnestic disorder associated with head trauma, which improves steadily in the months subsequent to the trauma. Amnesia secondary to processes that destroy brain tissue, such as stroke, tumor, and infection, are irreversible, although, again, static, after the acute infection or ischemia has been staunched. TREATMENT

The primary approach to treating amnestic disorders is to treat the underlying cause. Although a patient is amnestic, supportive prompts about the date, the time, and the patient’s location can be helpful and can reduce the patient’s anxiety. After resolution of the amnestic episode, psychotherapy of some type (cognitive, psychodynamic, or supportive) may help patients incorporate the amnestic experience into their lives. Psychotherapy Psychodynamic interventions may be of considerable value for patients who have amnestic disorders that result from insults to the brain. Understanding the course of recovery in such patients helps clinicians to be sensitive to the narcissistic injury inherent in damage to the CNS. The first phase of recovery, in which patients are incapable of processing what happened because the ego defenses are overwhelmed, requires clinicians to serve as a supportive auxiliary ego who explains to a patient what is happening and provides missing ego functions. In the second phase of recovery, as the realization of the injury sets in, patients may become angry and feel victimized by the malevolent hand of fate. They may view others, including the clinician, as bad or destructive, and clinicians must contain these projections without becoming punitive or retaliatory. Clinicians can build a therapeutic alliance with patients by explaining slowly and clearly what happened and by offering an explanation for a patient’s internal experience. The third phase of recovery is integrative. As a patient accepts what has happened, a clinician can help the patient form a new identity by connecting current experiences of the self with past experiences. Grieving over the lost faculties may be an important feature of the third phase. Most patients who are amnestic because of brain injury engage in denial. Clinicians must respect and empathize with the patient’s need to deny the reality of what has happened. Insensitive and blunt confrontations destroy any developing therapeutic alliance and can cause patients to feel attacked. In a sensitive approach, clinicians help patients accept

their cognitive limitations by exposing them to these deficits bit by bit over time. When patients fully accept what has happened, they may need assistance in forgiving themselves and any others involved, so that they can get on with their lives. Clinicians must also be wary of being seduced into thinking that all of the patient’s symptoms are directly related to the brain insult. An evaluation of preexisting personality disorders, such as borderline, antisocial, and narcissistic personality disorders, must be part of the overall assessment; many patients with personality disorders place themselves in situations that predispose them to injuries. These personality features may become a crucial part of the psychodynamic psychotherapy. Recently, centers for cognitive rehabilitation have been established whose rehabilitation-oriented therapeutic milieu is intended to promote recovery from brain injury, especially that from traumatic causes. Despite the high cost of extended care at these sites, which provide both long-term institutional and daytime services, no data have been developed to define therapeutic effectiveness for the heterogeneous groups of

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21.5 Neurocognitive and Other Disorders Due to a General Medical Condition

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or a consequence of deranged upbringing or environment (e.g., personality disorder), all mental disorders ultimately share one common underlying theme: aberration in brain function. Treatments for those conditions, whether psychological or biological, attempt to restore normal brain chemistry. The differential diagnosis for a mental syndrome in a patient should always include consideration of (1) any general medical condition that a patient may have and (2) any prescription, nonprescription, or illegal substances that a patient may be taking. Although some specific medical conditions have classically been associated with mental syndromes, a much larger number of general medical conditions have been associated with mental syndromes in case reports and small studies. The mental disorders caused by a general medical condition span the entire spectrum

of diagnostic categories. Thus, one can have a cognitive disorder, mood disorder, sleep disorder, anxiety disorder, and psychotic disorder to mention but a few that are caused or aggravated by a medical condition. In this section, neurocognitive disorders due to a general medical condition are described, including epilepsy, autoimmune disorders and AIDS, of which psychiatrists should be aware. SPECIFIC DISORDERS Epilepsy Epilepsy is the most common chronic neurological disease in the general population and affects approximately 1 percent of the population in the United States. For psychiatrists, the major concerns about epilepsy are consideration of an epileptic diagnosis in psychiatric patients, the psychosocial ramifications of a diagnosis of epilepsy for a patient, and the psychological and cognitive effects of commonly used anticonvulsant drugs. With regard to the first of these concerns, 30 to 50 percent of all persons with epilepsy have psychiatric difficulties sometime during the course of their illness. The most common behavioral symptom of epilepsy is a change in personality. Psychosis and violence occur much less commonly than was previously believed. Definitions. A seizure is a transient paroxysmal pathophysiological disturbance of cerebral function caused by a spontaneous, excessive discharge of neurons. Patients are said to have epilepsy if they have a chronic condition characterized by recurrent seizure. The ictus, or ictal event, is the seizure itself. The nonictal periods are categorized as preictal, postictal, and interictal. The symptoms during the ictal event are determined primarily by the site of origin in the brain for the seizure and by the pattern of the spread of seizure activity through the brain. Interictal symptoms are influenced by the ictal event and other neuropsychiatric and psychosocial factors, such as coexisting psychiatric or neurological disorders, the presence of psychosocial stressors, and premorbid personality traits. Classification. The two major categories of seizures are partial and generalized. Partial seizures involve epileptiform activity in localized brain regions. Generalized seizures involve the entire brain (Fig. 21.5-1). A classification system for seizures is outlined in Table 21.5-1.

FIGURE 21.5-1 Electroencephalographic recording during generalized tonic-clonic seizure showing rhythmic sharp waves and muscles artifact during tonic phase, spike and wave discharges during clonic phase, and attenuation of activity during postictal state. (Courtesy of Barbara F. Westmoreland, M.D.) Table 21.5-1 International Classification of Epileptic Seizures

GENERALIZED SEIZURES. Generalized tonic-clonic seizures exhibit the classic symptoms of loss of consciousness, generalized tonic-clonic movements of the limbs, tongue biting, and incontinence. Although the diagnosis of the ictal events of the seizure is relatively straightforward, the postictal state, characterized by a slow, gradual recovery of consciousness and cognition, occasionally presents a diagnostic dilemma for a psychiatrist in an emergency department. The recovery period

from a generalized tonicclonic seizure ranges from a few minutes to many hours, and the clinical picture is that of a gradually clearing delirium. The most common psychiatric problems associated with generalized seizures involve helping patients adjust to a chronic neurological disorder and assessing the cognitive or behavioral effects of anticonvulsant drugs. Absence Seizure (Petit Mal). A difficult type of generalized seizure for a psychiatrist to diagnose is an absence, or petit mal, seizure. The epileptic nature of the episodes may go unrecognized because the characteristic motor or sensory manifestations of epilepsy may be absent or so slight that they do not arouse suspicion. Petit mal epilepsy usually begins in childhood between the ages of 5 and 7 years and ceases by puberty. Brief disruptions of consciousness, during which the patient suddenly loses contact with the environment, are characteristic of petit mal epilepsy, but the patient has no true loss of consciousness and no convulsive movements during the episodes. The EEG produces a characteristic pattern of three-per-second spike-and-wave activity (Fig. 21.5-2). In rare instances, petit mal epilepsy begins in adulthood. Adult-onset petit mal epilepsy can be characterized by sudden, recurrent psychotic episodes or deliriums that appear and disappear abruptly. The symptoms may be accompanied by a history of falling or fainting spells.

FIGURE 21.5-2 Petit mal epilepsy characterized by bilaterally synchronous, 3-Hz spike and slow-wave activity. PARTIAL SEIZURES. Partial seizures are classified as either simple (without alterations in consciousness) or complex (with an alteration in consciousness). Somewhat more than half of all patients with partial seizures have complex partial seizures. Other terms used for complex partial seizures are temporal lobe epilepsy, psychomotor seizures, and limbic epilepsy; these terms, however, are not accurate descriptions of the clinical situation. Complex partial epilepsy, the most common form of epilepsy in adults, affects approximately three of 1,000 persons. About 30 percent of patients with complex partial seizures have major mental illness such as depression. SYMPTOMS PREICTAL SYMPTOMS. Preictal events (auras) in complex partial epilepsy include autonomic sensations (e.g., fullness in the stomach, blushing, and changes in respiration); cognitive sensations (e.g., déjá vu, jamais vu, forced thinking, dreamy states); affective states (e.g., fear, panic, depression, elation); and, classically, automatisms (e.g., lip smacking, rubbing, chewing). ICTAL SYMPTOMS. Brief, disorganized, and uninhibited behavior characterizes the ictal event. Although some defense attorneys may claim otherwise, rarely does a person exhibit organized, directed violent behavior during an epileptic episode. The cognitive symptoms include amnesia for the time during the seizure and a period of resolving delirium after the seizure. A seizure focus can be found on an EEG in 25 to 50 percent of all patients with complex partial epilepsy (Fig. 21.5-3). The use of sphenoidal or anterior temporal electrodes and sleep-deprived EEGs may increase the likelihood of finding an EEG abnormality. Multiple normal EEGs are often obtained for a patient with complex partial epilepsy; therefore, normal EEGs cannot be used to exclude a

diagnosis of complex partial epilepsy. The use of long-term EEG recordings (usually 24 to 72 hours) can help clinicians detect a seizure focus in some patients. Most studies show that the use of nasopharyngeal leads does not add much to the sensitivity of an EEG, but they do add to the discomfort of the procedure for the patient. FIGURE 21.5-3 An interictal encephalograph in a patient with complex partial seizures reveals frequent left temporal spike discharges and rare, independent right temporal sharp-wave activity. (From Cascino GD. Complex partial seizures: clinical features and differential diagnosis. Psychiatr Clin North Am. 1992;15:377, with permission.) INTERICTAL SYMPTOMS Personality Disturbances. The most frequent psychiatric abnormalities

reported in patients with epilepsy are personality disorders, and they are especially likely to occur in patients with epilepsy of temporal lobe origin. The most common features are religiosity, a heightened experience of emotions—a quality usually called viscosity of personality—and changes in sexual behavior. The syndrome in its complete form is relatively rare even in those with complex partial seizures of temporal lobe origin. Many patients are not affected by personality disturbances; others have a variety of disturbances that differ strikingly from the classic syndrome. A striking religiosity may be manifested not only by increased participation in overtly religious activities but also by unusual concern for moral and ethical issues, preoccupation with right and wrong, and heightened interest in global and philosophical concerns. The hyperreligious features can sometimes seem like the prodromal symptoms of schizophrenia and can result in a diagnostic problem in an adolescent or a young adult.

The symptom of viscosity of personality is usually most noticeable in a patient’s conversation, which is likely to be slow, serious, ponderous, pedantic, overly replete with nonessential details, and often circumstantial. The listener may grow bored but be unable to find a courteous and successful way to disengage from the conversation. The speech tendencies, often mirrored in the patient’s writing, result in a symptom known as hypergraphia, which some clinicians consider virtually pathognomonic for complex partial epilepsy. Changes in sexual behavior may be manifested by hypersexuality; deviations in sexual interest, such as fetishism and transvestism; and, most commonly, hyposexuality. The hyposexuality is characterized both by a lack of interest in sexual matters and by reduced sexual arousal. Some patients with the onset of complex partial epilepsy before puberty may fail to reach a normal level of sexual interest after puberty, although this characteristic may not disturb the patient. For patients with the onset of complex partial epilepsy after puberty, the change in sexual interest may be bothersome and worrisome. Psychotic Symptoms. Interictal psychotic states are more common than ictal psychoses. Schizophrenia-like interictal episodes can occur in patients with epilepsy, particularly those with temporal lobe origins. An estimated 10 percent of all patients with complex partial epilepsy have psychotic symptoms. Risk factors for the symptoms include female gender, left-handedness, the onset of seizures during puberty, and a left-sided lesion. The onset of psychotic symptoms in epilepsy is variable. Classically, psychotic symptoms appear in patients who have had epilepsy for a long time, and the onset of psychotic symptoms is preceded by the development of personality changes related to the epileptic brain activity. The most characteristic symptoms of the psychoses are hallucinations and paranoid delusions. Patients usually remain warm and appropriate in affect, in contrast to the abnormalities of affect commonly seen in patients with schizophrenia. The thought disorder symptoms in patients with psychotic epilepsy are most commonly those involving conceptualization and circumstantiality rather than the classic schizophrenic symptoms of blocking and looseness. Violence. Episodic violence has been a problem in some patients with epilepsy, especially epilepsy of temporal and frontal lobe origin. Whether the violence is a manifestation of the seizure itself or is of interictal psychopathological origin is uncertain. Most evidence points to the extreme rarity of violence as an ictal phenomenon. Only in rare cases should violence in the patient with epilepsy be attributed to the seizure itself. Mood Disorder Symptoms. Mood disorder symptoms, such as depression and mania, are seen less often in epilepsy than are schizophrenia-like symptoms. The mood disorder symptoms that do occur tend to be episodic and appear most often when the epileptic foci affect the temporal lobe of the nondominant cerebral hemisphere. The importance of mood disorder symptoms may be attested to by the increased incidence of attempted suicide in people with epilepsy. Diagnosis. A correct diagnosis of epilepsy can be

particularly difficult when the ictal and interictal symptoms of epilepsy are severe manifestations of psychiatric symptoms in the absence of significant changes in consciousness and cognitive abilities. Psychiatrists, therefore, must maintain a high level of suspicion during the evaluation of

a new patient and must consider the possibility of an epileptic disorder even in the absence of the classic signs and symptoms. Another differential diagnosis to consider is pseudoseizure, in which a patient has some conscious control over mimicking the symptoms of a seizure (Table 21.5-2). Table 21.5-2 Differentiating Features of Pseudoseizures and Epileptic Seizures For patients who have previously received a diagnosis of epilepsy, the appearance of new psychiatric symptoms should be considered as possibly representing an evolution in their epileptic symptoms. The appearance of psychotic symptoms, mood disorder symptoms, personality changes, or symptoms of anxiety (e.g., panic attacks) should cause a clinician to evaluate the control of the patient's epilepsy and to assess the patient for the presence of an independent mental disorder. In such circumstances, the clinician should evaluate the patient's compliance with the anticonvulsant drug regimen and should consider whether the psychiatric symptoms could be adverse effects from the antiepileptic drugs themselves. When psychiatric symptoms appear in a patient who has had epilepsy diagnosed or considered as a diagnosis in the past, the clinician should obtain results of one or more EEG examinations. In patients who have not previously received a diagnosis of epilepsy, four characteristics should cause a clinician to be suspicious of the possibility: the abrupt onset of psychosis in a person previously regarded as psychologically healthy, the abrupt onset of delirium without a recognized cause, a history of similar episodes with abrupt onset and spontaneous recovery, and a history of previous unexplained falling or fainting spells. Treatment. First-line drugs for generalized tonic-clonic seizures are valproate and

phenytoin (Dilantin). First-line drugs for partial seizures include carbamazepine, oxcarbazepine (Trileptal), and phenytoin. Ethosuximide (Zarontin) and valproate are first-line drugs for absence (petit mal) seizures. The drugs used for various types of seizures are listed in Table 21.5-3. Carbamazepine and valproic acid may be helpful in controlling the symptoms of irritability and outbursts of aggression, as are the typical antipsychotic drugs. Psychotherapy, family counseling, and group therapy may be useful in addressing the psychosocial issues associated with epilepsy. In addition, clinicians should be aware that many antiepileptic drugs cause mild to moderate cognitive impairment, and an adjustment of the dosage or a change in medications should be considered if symptoms of cognitive impairment are a problem in a patient. Table 21.5-3 Commonly Used Anticonvulsant Drugs Brain Tumors Brain tumors and cerebrovascular diseases can cause virtually any psychiatric symptom or syndrome, but cerebrovascular diseases, by the nature of their onset and symptom pattern, are rarely misdiagnosed as mental disorders. In general, tumors are associated with fewer psychopathological signs and symptoms than are cerebrovascular diseases affecting a similar volume of brain tissue. The two key approaches to the diagnosis of either condition are a comprehensive clinical history and a complete neurological examination. Performance of the appropriate brain imaging technique is usually the final diagnostic procedure; the imaging should confirm the clinical diagnosis. Clinical Features, Course, and Prognosis. Mental symptoms are experienced at some time during the course of illness in approximately 50 percent of patients with brain tumors. In approximately 80 percent of these patients with mental symptoms, the tumors are located in frontal or limbic brain regions rather than in parietal or temporal regions. Whereas meningiomas are likely to cause focal symptoms by compressing a limited region of the cortex, gliomas are likely to cause diffuse symptoms. Delirium is most often a

component of rapidly growing, large, or metastatic tumors. If a patient's

history and a physical examination reveal bowel or bladder incontinence, a frontal lobe tumor should be suspected; if the history and examination reveal abnormalities in memory and speech, a temporal lobe tumor should be suspected. COGNITION. Impaired intellectual functioning often accompanies the presence of a brain tumor, regardless of its type or location. LANGUAGE SKILLS. Disorders of language function may be severe, particularly if tumor growth is rapid. In fact, defects of language function often obscure all other mental symptoms. MEMORY. Loss of memory is a frequent symptom of brain tumors. Patients with brain tumors exhibit Korsakoff's syndrome and retain no memory of events that occurred since the illness began. Events of the immediate past, even painful ones, are lost. Patients, however, retain old memories and are unaware of their loss of recent memory. PERCEPTION. Prominent perceptual defects are often associated with behavioral disorders, especially because patients must integrate tactile, auditory, and visual perceptions to function normally. AWARENESS. Alterations of consciousness are common late symptoms of increased intracranial pressure caused by a brain tumor. Tumors arising in the upper part of the brainstem can produce a unique symptom called akinetic mutism, or vigilant coma. The patient is immobile and mute yet alert. Colloid Cysts. Although they are not brain tumors, colloid cysts located in the third ventricle can exert physical pressure on structures within the diencephalon and produce such mental symptoms as depression, emotional lability, psychotic symptoms, and personality changes. The classic associated neurological symptoms are positiondependent intermittent headaches. Head Trauma Head trauma can result in an array of mental symptoms and lead to a diagnosis of dementia due to head trauma or to mental disorder not otherwise specified due to a general medical condition (e.g., postconcussional disorder). The postconcussive syndrome remains controversial because it focuses on the wide range of psychiatric symptoms, some serious, that can follow what seems to be minor head trauma. Pathophysiology. Head trauma is a common clinical situation; an estimated 2 million incidents involve head trauma each year. Head trauma most commonly occurs in people 15 to 25 years of age and has a male-to-female predominance of approximately 3 to 1. Gross estimates based on the severity of the head trauma suggest that virtually all patients with serious head trauma, more than half of patients with moderate head trauma, and about 10 percent of patients with mild head trauma have ongoing neuropsychiatric sequelae resulting from the head trauma. Head trauma can be divided

grossly into penetrating head trauma (e.g., trauma produced by a bullet) and blunt trauma, in which there is no physical penetration of the skull. Blunt trauma is far more common than penetrating head trauma. Motor vehicle accidents account for more than half of all the incidents of blunt CNS trauma; falls, violence, and sports-related head trauma account for most of the remaining cases (Fig. 21.5-4). FIGURE 21.5-4 Severe contusion of the frontal poles has resulted in their atrophy and distortion. (Courtesy of Dr. H. M. Zimmerman.) Whereas brain injury from penetrating wounds is usually localized to the areas directly affected by the missile, brain injury from blunt trauma involves several mechanisms. During the actual head trauma, the head usually moves back and forth violently, so that the brain hits repeatedly against the skull as it and the skull are mismatched in their rapid deceleration and acceleration. This crashing results in focal contusions, and the stretching of the brain parenchyma produces diffuse axonal injury. Later developing processes, such as edema and hemorrhaging, can result in further damage to the brain. Symptoms. The two major clusters of symptoms related to head trauma are those of cognitive impairment and of behavioral sequelae. After a period of posttraumatic amnesia, there is usually a

6- to 12-month period of recovery, after which the remaining

symptoms are likely to be permanent. The most common cognitive problems are decreased speed in information processing, decreased attention, increased distractibility, deficits in problem-solving and in the ability to sustain effort, and problems with memory and learning new information. A variety of language disabilities can also occur. Behaviorally, the major symptoms involve depression, increased impulsivity, increased aggression, and changes in personality. These symptoms can be further exacerbated by the use of alcohol, which is often involved in the head trauma event itself. A debate has ensued about how preexisting character and personality traits affect the development of behavioral symptoms after head trauma. The critical studies needed to answer the question definitively have not yet been done, but the weight of opinion is leaning toward a biologically and neuroanatomically based association between the head trauma and the behavioral sequelae. Treatment. The treatment of the cognitive and behavioral disorders in patients with head trauma is basically similar to the treatment approaches used in other patients with these symptoms. One difference is that patients with head trauma may be particularly susceptible to the side effects associated with psychotropic drugs; therefore, treatment with these agents should be initiated in lower dosages than usual, and they should be titrated upward more slowly than usual. Standard antidepressants can be used to treat depression, and either anticonvulsants or antipsychotics can be used to treat aggression and impulsivity. Other approaches to the symptoms include lithium, calcium channel blockers, and β-adrenergic receptor antagonists. Clinicians must support patients through individual or group psychotherapy and should support the major caretakers through couples and family therapy. Patients with minor and moderate head trauma often rejoin their families and restart their jobs; therefore, all involved parties need help to adjust to any changes in the patient’s personality and mental abilities. Demyelinating Disorders Multiple sclerosis (MS) is the major demyelinating disorder. Other demyelinating disorders include amyotrophic lateral sclerosis (ALS), metachromatic leukodystrophy, adrenoleukodystrophy, gangliosidoses, subacute sclerosing panencephalitis, and Kufs’ disease. All of these disorders can be associated with neurological, cognitive, and behavioral symptoms. Multiple Sclerosis. MS is characterized by multiple episodes of symptoms, pathophysiologically related to multifocal lesions in the white matter of the CNS (Fig. 21.5-5). The cause remains unknown, but studies have focused on slow viral infections and disturbances in the immune system. The estimated prevalence of MS in the Western Hemisphere is 50 per 100,000 people. The disease is much more frequent in cold and temperate climates than in the tropics and subtropics and more common in women than

in men; it is predominantly a disease of young adults. In most patients, the onset occurs between the ages of 20 and 40 years. FIGURE 21.5-5 Multiple sclerosis. Irregular, seemingly punched out zones of demyelination are evident in this section through the level of the fourth ventricle. Myelin stain. 2.6×. (Courtesy of Dr. H. M. Zimmerman.) The neuropsychiatric symptoms of MS can be divided into cognitive and behavioral types. Research reports have found that 30 to 50 percent of patients with MS have mild cognitive impairment and that 20 to 30 percent of them have serious cognitive impairments. Although evidence indicates that patients with MS experience a decline in their general intelligence, memory is the most commonly affected cognitive function. The severity of the memory impairment does not seem to be correlated with the severity of the neurological symptoms or the duration of the illness. The behavioral symptoms associated with MS are varied and can include euphoria, depression, and personality changes. Psychosis is a rare complication.

Approximately 25 percent of persons with MS exhibit a euphoric mood that is not hypomanic but somewhat more cheerful than their situation warrants and not necessarily in character with their disposition before the onset of MS. Only 10 percent of patients with MS have a sustained and elevated mood, although it is still not truly hypomanic. Depression, however, is common; it affects 25 to 50 percent of patients with MS and results in a higher rate of suicide than is seen in the general population. Risk factors for suicide in patients with MS are male sex, onset of MS before age 30 years, and a relatively recent diagnosis of the disorder. Personality changes are also common in patients with MS; they affect 20 to 40 percent of patients and are often characterized by increased irritability or apathy. Amyotrophic Lateral Sclerosis. ALS is a progressive, noninherited disease of asymmetrical muscle atrophy. It begins in adult life and progresses over months or years to involve all the striated muscles except the cardiac and ocular muscles. In addition to muscle atrophy, patients have signs of pyramidal tract involvement. The illness is rare and occurs in approximately 1.6 persons per 100,000 annually. A few patients have concomitant dementia. The disease progresses rapidly, and death generally occurs

within 4 years of onset. Infectious Diseases Herpes Simplex Encephalitis. Herpes simplex encephalitis, the most common type of focal encephalitis, most commonly affects the frontal and temporal lobes. The symptoms often include anosmia, olfactory and gustatory hallucinations, and personality changes and can also involve bizarre or psychotic behaviors. Complex partial epilepsy may also develop in patients with herpes simplex encephalitis. Although the mortality rate for the infection has decreased, many patients exhibit personality changes, symptoms of memory loss, and psychotic symptoms. Rabies Encephalitis. The incubation period for rabies ranges from 10 days to 1 year, after which symptoms of restlessness, overactivity, and agitation can develop. Hydrophobia, present in up to 50 percent of patients, is characterized by an intense fear of drinking water. The fear develops from the severe laryngeal and diaphragmatic spasms that the patients experience when they drink water. When rabies encephalitis develops, the disease is fatal within days or weeks. Neurosyphilis. Neurosyphilis (also known as general paresis) appears 10 to 15 years after the primary Treponema infection. Since the advent of penicillin, neurosyphilis has become a rare disorder, although AIDS is associated with reintroducing neurosyphilis into medical practice in some urban settings. Neurosyphilis generally affects the frontal lobes and results in personality changes, development of poor judgment, irritability, and decreased care for self. Delusions of grandeur develop in 10 to 20 percent of affected patients. The disease progresses with the development of dementia and tremor until patients are paretic. The neurological symptoms include Argyll-Robertson pupils, which are small, irregular, and unequal and have light-near reflex dissociation, tremor, dysarthria, and hyperreflexia. Cerebrospinal fluid (CSF) examination shows lymphocytosis, increased protein, and a positive result on a Venereal Disease Research Laboratory (VDRL) test. Chronic Meningitis. Chronic meningitis is now seen more often than in the recent past because of the immunocompromised condition of people with AIDS. The usual causative agents are Mycobacterium tuberculosis, Cryptococcus spp., and Coccidioides spp. The usual symptoms are headache, memory impairment, confusion, and fever. Subacute Sclerosing Panencephalitis. Subacute sclerosing panencephalitis is a disease of childhood and early adolescence, with a 3-to-1 male-to-female ratio. The onset usually follows either an infection with measles or a vaccination for measles. The initial symptoms may be behavioral change, temper tantrums, sleepiness, and hallucinations, but the classic symptoms of myoclonus, ataxia, seizures, and intellectual deterioration eventually develop. The disease progresses relentlessly to coma and death in 1 to 2

years. Lyme Disease. Lyme disease is caused by infection with the spirochete Borrelia burgdorferi transmitted through the bite of the deer tick (Ixodes scapularis), which feeds on infected deer and mice. About 16,000 cases are reported annually in the United States. A characteristic bull's-eye rash (Fig. 21.5-6) is found at the site of the tick bite followed shortly thereafter by flulike symptoms. Impaired cognitive functioning and mood changes are associated with the illness and may be the presenting complaint. These include memory lapses, difficulty concentrating, irritability, and depression. FIGURE 21.5-6 Erythema migrans ("bull's-eye" rash) on the thigh. (From Barbour R. Lyme disease. In: Hoeprich PD, Jordan MC, Ronald AR, eds. Infectious Diseases: A Treatise of Infectious Processes. Philadelphia: JB Lippincott; 1994:1329, with permission.) No clear-cut diagnostic test is available. About 50 percent of patients become seropositive to B. burgdorferi. Prophylaxis vaccine is not always effective and is controversial. Treatment consists of a 14- to 21-day course of doxycycline (Vibramycin), which results in a 90 percent cure rate. Specific psychotropic drugs can be targeted to treat the psychiatric sign or symptom (e.g., diazepam [Valium] for anxiety). Left untreated, about 60 percent of persons develop a chronic condition. Such patients may

be given an erroneous diagnosis of a primary depression rather than one secondary to the medical condition. Support groups for patients with chronic Lyme disease are important. Group members provide each other with emotional support that helps improve their quality of life. Prion Disease. Prion disease is a group of related disorders caused by a transmissible infectious protein known as a prion. Included in this group are CreutzfeldtJakob disease (CJD), Gerstmann-Straussler-Scheinker disorder (GSS), fatal familial insomnia (FFI), and kuru. A variant of CJD (vCJD), also called "mad cow disease," appeared in 1995 in the United Kingdom and is attributed to the transmission of bovine spongiform encephalopathy (BSE) from cattle to humans. Collectively, these disorders are also known as subacute spongiform encephalopathy because of shared neuropathological changes that consist of (1) spongiform vacuolization, (2) neuronal loss, and (3) astrocyte proliferation in the cerebral cortex. Amyloid plaques may or may not be present. ETIOLOGY. Prions are transmissible agents but differ from viruses in that they lack nucleic acid. Prions are mutated proteins generated from the human prion protein gene (PrP), which is located on the short arm of chromosome 20. No direct link exists between prion disease and Alzheimer's disease, which has been traced to chromosome 21. The PrP mutates into a disease-related isoform PrP-Super-C (PrPSc), which can replicate and is infectious. The neuropathological changes that occur in prion disease are presumed to be caused by direct neurotoxic effects of PrPSc. The specific prion disease that develops depends on the mutation of PrP that occurs. Mutations at PrP 178N/129V cause CJD, mutations at 178N/129M cause FFI, and mutations at 102L/129M cause GSS and kuru. Other mutations of PrP have been described, and research continues in this important area of genomic identification. Some mutations are both fully penetrant and autosomal dominant and account for inherited forms of prion disease. For example, both GSS and FFI are inherited disorders, and about 10 percent of cases of CJD are also inherited. Prenatal testing for the abnormal PrP gene is available; whether or not such testing should be routinely done is open to question at this time. CREUTZFELDT-JAKOB DISEASE. First described in 1920, CJD is an invariably fatal, rapidly progressive disorder that occurs mainly in middle-aged or older adults. It manifests initially with fatigue, flulike symptoms, and cognitive impairment. As the disease progresses, focal neurological findings such as aphasia and apraxia occur. Psychiatric manifestations are protean and include emotional lability, anxiety, euphoria, depression, delusions, hallucinations, or marked personality changes. The disease progresses over months, leading to dementia, akinetic mutism, coma, and

death. The rates of CJD range from one to two cases per 1 million persons a year worldwide. The infectious agent self-replicates and can be transmitted to humans by inoculation with infected tissue and sometimes by ingestion of contaminated food. Iatrogenic

transmission has been reported via transplantation of contaminated cornea or dura mater or to children via contaminated supplies of human growth hormone derived from infected persons. Neurosurgical transmission has also been reported. Household contacts are not at greater risk for developing the disease than the general population unless there is direct inoculation. Diagnosis requires pathological examination of the cortex, which reveals the classic triad of spongiform vacuolation, loss of neurons, and astrocyte cell proliferation. The cortex and basal ganglia are most affected. An immunoassay test for CJD in the CSF shows promise in supporting the diagnosis; however, this needs to be tested more extensively. Although not specific for CJD, EEG abnormalities are present in nearly all patients, consisting of a slow and irregular background rhythm with periodic complex discharges. CT and MRI studies may reveal cortical atrophy later in the course of disease. SPECT and positron emission tomography (PET) reveal heterogeneously decreased uptake throughout the cortex. No known treatment exists for CJD. Death usually occurs within 6 months after diagnosis. VARIANT CJD. In 1995, a variant of CJD (vCJD) appeared in the United Kingdom. The patients affected all died; they were young (younger than age 40 years), and none had risk factors of CJD. At autopsy, prion disease was found. The disease was attributed to the transmission in the United Kingdom of BSE between cattle and from cattle to humans in the 1980s. BSE appears to have originated from sheep scrapie–contaminated feed given to cattle. Scrapie is a spongiform encephalopathy found in sheep and goats that has not been shown to cause human disease; however, it is transmissible to other animal species. The mean age of onset is 29 years, and about 150 people worldwide had been infected as of 2006. Clinicians must be alert to the diagnosis in young people with behavioral and psychiatric abnormalities in association with cerebellar signs such as ataxia or myoclonus. The psychiatric presentation of vCJD is not specific. Most patients have reported depression, withdrawal, anxiety, and sleep disturbance. Paranoid delusions have occurred. Neuropathological changes are similar to those in vCJD, with the addition of amyloid plaques. Epidemiological data are still being gathered. The incubation period for vCJD and the amount of infected meat product required to cause infection are unknown. One patient was reported to have been a vegetarian for 5 years before his disease was diagnosed. vCJD can be diagnosed antemortem by examining the tonsils with Western blot immunostains to detect PrPSc in lymphoid tissue. Diagnosis relies on the development of progressive neurodegenerative features in persons who have ingested contaminated meat or brains. No cure exists, and death usually occurs within 2 to 3 years after diagnosis. Prevention is dependent on careful monitoring of cattle for disease and feeding them grain instead of meat byproducts. KURU. Kuru is an epidemic prion disease found in New Guinea that is caused by cannibalistic funeral rituals in which the brains of the deceased are eaten. Women are

more affected by the disorder than men, presumably because they participate in the ceremony to a greater extent. Death usually occurs within 2 years after symptoms develop. Neuropsychiatric signs and symptoms consist of ataxia, chorea, strabismus, delirium, and dementia. Pathological changes are similar to those with other prion disease: neuronal loss, spongiform lesions, and astrocytic proliferation. The cerebellum is most affected. Iatrogenic transmission of kuru has occurred when cadaveric material such as dura mater and corneas were transplanted into normal recipients. Since the cessation of cannibalism in New Guinea, the incidence of the disease has

decreased drastically. GERSTMANN-STRAUSSLER-SCHEINKER DISEASE. First described in 1928, GSS is a neurodegenerative syndrome characterized by ataxia, chorea, and cognitive decline leading to dementia. It is caused by a mutation in the PrP gene that is fully penetrant and autosomal dominant; thus, the disease is inherited, and affected families have been identified over several generations. Genetic testing can confirm the presence of the abnormal genes before onset. Pathological changes characteristic of prion disease are present: spongiform lesions, neuronal loss, and astrocyte proliferation. Amyloid plaques have been found in the cerebellum. Onset of the disease occurs between 30 and 40 years of age. The disease is fatal within 5 years of onset. FATAL FAMILIAL INSOMNIA. FFI is an inherited prion disease that primarily affects the thalamus. A syndrome of insomnia and autonomic nervous system dysfunction consisting of fever, sweating, labile blood pressure, and tachycardia occurs that is debilitating. Onset is in middle adulthood, and death usually occurs in 1 year. No treatment currently exists. FUTURE DIRECTIONS. Determining how prions mutate to produce disease phenotypes and determining how they are transmitted between different mammalian species are major areas of research. Public health measures to prevent transmission of animal disease to humans are ongoing and must be relentless, especially because these disorders are invariably fatal within a few years of onset. Developing genetic interventions that prevent or repair damage to the normal prion gene offers the best hope of cure. Psychiatrists are faced with having to manage cases of persons who actually have the disease and those with hypochondriacal fears of having contracted the disease. In some patients, such fears can reach delusional proportions. Treatment is symptomatic and involves anxiolytics, antidepressants, and psychostimulants, depending on symptoms. Supportive psychotherapy may be of use in early stages to help patients and family cope with the illness. Preventing unintentional human-to-human or animal-to-human transmission of prions remains the best way to limit the scope of these diseases. Sporadic cases of CJD will still appear, however, because of the rare spontaneous mutation of the normal prion protein into the abnormal form. At present, little exists to offer patients with prion disease other than supportive treatment and emotional support.

Immune Disorders The major immune disorders in contemporary society is HIV and AIDS, but other immune disorders such as lupus erythematosus and autoimmune disorders that affect brain neurotransmitters (discussed below) can also present diagnostic and treatment challenges to mental health clinicians. HIV Infection and AIDS HIV is a retrovirus related to the human T-cell leukemia viruses (HTLV) and to retroviruses that infect animals, including nonhuman primates. At least two types of HIV have been identified, HIV-1 and HIV-2. HIV-1 is the causative agent for most HIVrelated diseases; HIV-2, however seems to be causing an increasing number of infections in Africa. Other types of HIV may exist, which are now classified as HIV-O. HIV is present in blood; semen; cervical and vaginal secretions; and, to a lesser extent, in saliva, tears, breast milk, and the CSF of those who are infected. HIV is most often transmitted through sexual intercourse or the transfer of contaminated blood from one person to another. Health providers should be aware of the guidelines for safe sexual practices and should advise their patients to practice safe sex (Table 21.5-4). The Centers for Disease Control and Prevention guidelines for the prevention of HIV from infected to uninfected persons is listed in Table 21.5-5. Table 21.5-5 Centers for Disease Control and Prevention Guidelines for the Prevention of HIV Transmission from Infected to Uninfected Persons

Table 21.5-4 AIDS Safe-Sex Guidelines

After infection with HIV, AIDS is estimated to develop in 8 to 11 years, although this time is gradually increasing because of early treatment. When a person is infected with HIV, the virus primarily targets T4 (helper) lymphocytes, socalled CD4+ lymphocytes, to which the virus binds because of a glycoprotein (gp120) on the viral surface has a high affinity for the CD4 receptor on T4 lymphocytes. After binding, the virus can inject its ribonucleic acid (RNA) into the infected lymphocyte, where the RNA is transcribed into deoxyribonucleic acid (DNA) by the action of reverse transcriptase. The resultant DNA can then be incorporated ino the host cell's genome and translated and eventually transcribed when the lymphocyte is stimulated to divide. After viral proteins have been produced by lymphocytes, the various components of the virus assemble, and new mature viruses bud off from the host cell. Diagnosis SERUM TESTING. Techniques are now widely available to detect the presence of anti-HIV antibodies in human. The conventional test uses blood (time to result, 3 to 10 days) and the rapid test uses an oral swab (time to result, 20 minutes). Both tests are 99.9 percent sensitive and specific. Health care workers and their patients must understand that the presence of HIV antibodies indicate infection, not immunity to infection. Those who test positive have been exposed to the virus, have the virus within their bodies, have the potential to transmit the virus to another person, and will almost certainly eventually develop AIDS. Those who test negative have either not been exposed to the HIV virus and are not infected or were exposed to the HIV virus but have not yet developed the antibodies, which is a possibility if the exposure occurred less than 1 year before testing. Seroconversion most commonly occurs 6 to 12 weeks after infection, although in rare

cases seroconversion can take 6 to 12 months. COUNSELING. Although specific groups of persons are at high risk for contracting HIV and should be tested, any person who wants to be tested should probably be tested. The reason for requesting a test should be ascertained to detect unspoken concerns and motivations that may merit psychotherapeutic intervention. Past practices that may have put the testee at risk for HIV infection and safe sexual practices should be discussed. During posttest counseling, counselors should explain that a negative test finding implies that safe sexual behavior and the avoidance of shared hypodermic needles are recommended for the person to remain free of HIV infection. Those with positive results must receive counseling about safe practices and potential treatment options. They may need additional psychotherapeutic interventions if anxiety or depressive disorders develop after they discover that they are infected. A person may react to a positive HIV test finding with a syndrome similar to posttraumatic stress disorder. Adjustment disorder with anxiety or depressed mood may develop in as many as 25 percent of those informed of a positive HIV test result. CONFIDENTIALITY. No one should be given an HIV test without previous knowledge and consent, although various jurisdictions and organizations, such as the military, now require HIV testing for all inhabitants or members. The results of an HIV test can be shared with other members of a medical team, although the information should be provided to no one else except for special circumstances. The patient should be advised against disclosing the result of HIV testing too readily to employers, friends, and family members; the information could result in discrimination in employment, housing, and insurance. The major exception to restriction of disclosure is the need to notify potential and past sexual or IV substance use partners. If a treating physician knows that a patient who is HIV infected is putting another person at risk of becoming infected, the physician may try either to hospitalize the infected person involuntarily (to prevent danger to others) or to notify the potential victim. Clinicians should be aware of the laws about such issues, which vary among the states. These guidelines also apply to inpatient psychiatric wards when a patient with HIV infection is believed to be sexually active

with other patients. Clinical Features NON-NEUROLOGICAL FACTORS. About 30 percent of persons infected with HIV experience a flulike syndrome 3 to 6 weeks after becoming infected; most never notice any symptoms immediately or shortly after their infection. The flulike syndrome includes fever, myalgia, headaches, fatigue, GI symptoms, and sometimes a rash. The syndrome may be accompanied by splenomegaly and lymphadenopathy. The most common infection in persons affected with HIV who have AIDS is Pneumocystis carinii pneumonia, which is characterized by a chronic, nonproductive cough, and dyspnea, sometimes sufficiently severe to result in hypoxemia and its resultant cognitive effects. For psychiatrists, the importance of these non-neurological,

nonpsychiatric complications lies in their biological effects on patients' brain function (e.g., hypoxia in P. carinii pneumonia) and their psychological effects on patients' moods and anxiety states. NEUROLOGICAL FACTORS. An extensive array of disease processes can affect the brain of a patient infected with HIV (Table 21.5-6). The most important diseases for mental health workers to be aware of are HIV mild neurocognitive disorder and HIV-associated dementia. Table 21.5-6 Conditions Associated with Human Immunodeficiency Virus (HIV) Infection PSYCHIATRIC SYNDROMES. HIV-associated dementia presents with the typical triad of symptoms seen in other subcortical dementias—memory and psychomotor speed impairments, depressive symptoms, and movement disorders. Patients may initially notice slight problems with reading, comprehension, memory, and mathematical skills, but these symptoms are subtle and may be overlooked or discounted as fatigue and illness. The Modified HIV Dementia Scale is a useful bedside screen and can be

administered serially to document disease progression. The development of dementia in HIV-infected patients is generally a poor prognostic sign, and 50 to 75 percent of patients with dementia die within 6 months. HIV-associated neurocognitive disorder (also known as HIV encephalopathy) is characterized by impaired cognitive functioning and reduced mental activity that interferes with work, domestic, and social functioning. No laboratory findings are specific to the disorder, and it occurs independently of depression and anxiety. Progression to HIV-associated dementia usually occurs but may be prevented by early treatment. Delirium can result from the same causes that lead to dementia in patients with HIV. Clinicians have classified delirious states characterized by both increased and decreased activity. Delirium in patients infected with HIV is probably underdiagnosed, but it should always precipitate a medical workup of a patient infected with HIV to determine whether a new CNS-related process has begun. Patients with HIV infection may have any of the anxiety disorders, but generalized anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder (OCD) are particularly common. Adjustment disorder with anxiety or depressed mood has been reported in 5 to 20 percent of HIV-infected patients. The incidence of adjustment disorder in HIV-infected patients is higher than usual in some special populations, such as military recruits and prison inmates. Depression is a significant problem in HIV and AIDS. Approximately 4 to 40 percent of HIV-infected patients meet the criteria for depressive disorders. Major depression is a risk factor for HIV infection by virtue of its impact on behavior, intensification of substance abuse, exacerbation of self-destructive behaviors, and promotion for poor partner choice in relationships. The pre-HIV infection prevalence of depressive disorders may be higher than usual in some groups who are at risk for contracting HIV. Depression has been shown to hinder effective treatment in infected persons. Patients with major depression are at increased risk for disease progression and death. HIV increases the risk of developing major depression through a variety of mechanisms, including direct injury to subcortical areas of the

brain, chronic stress, worsening social isolation, and intense demoralization. Depression is higher in women than in men. Mania can occur at any stage of HIV infection for individuals with preexisting bipolar disorder. AIDS mania is a type of mania that most commonly occurs in late-stage HIV infections and is associated with cognitive impairment. AIDS mania has a somewhat different clinical profile than bipolar mania. Patients tend to have cognitive slowing or dementia, and irritability is more characteristic than euphoria. AIDS mania is usually quite severe in its presentation and malignant in its course. It seems to be more chronic than episodic, has infrequent spontaneous remissions, and usually relapses with cessation of treatment. One clinically significant presentation is the delusional belief that one has discovered the cure for HIV or has been cured, which may result in high-risk behaviors and the spread of the HIV infection. Substance abuse is a primary vector for the spread of HIV. This impact is directed not

only at those who use IV drugs and their sexual partners but also at those who are disinhibited or cognitively impaired by intoxication and are driven by addiction to impulsive behaviors and unsafe sexual practices. Ongoing substance abuse has grave medical implications for HIV-infected patients. The accumulation of medical sequelae from chronic substance abuse can accelerate the process of immunocompromise and amplify the progressive burdens of the HIV infection itself. In addition to the direct physical effects cause by drugs, active substance use is highly associated with both nonadherence and reduced access to antiretroviral medication. Suicidal ideation and suicide attempts may increase in patients with HIV infection and AIDS. The risk factors for suicide among persons infected with HIV are having friends who died from AIDS, recent notification of HIV seropositivity, relapses, difficult social issues relating to homosexuality, inadequate social and financial support, and the presence of dementia or delirium. Psychotic symptoms are usually later-stage complications of HIV infection. They require immediate medical and neurological evaluation and often require management with antipsychotic medications. The worried well are persons in high-risk groups who, although they tested negative and are disease free, are anxious about contracting the virus. Some are reassured by repeated negative test results, but others cannot be reassured. Their worry well status can progress quickly to generalized anxiety disorder, panic attacks, OCD, and hypochondriasis. Treatment. Prevention is the primary approach to HIV infection. Primary prevention involves protecting persons from getting the disease; secondary prevention involves modification of the disease’s course. All persons with any risk of HIV infection should be informed about safe-sex practices and about the necessity to avoid sharing contaminated hypodermic needles. The assessment of patients infected with HIV should include a complete sexual and substance-abuse history, a psychiatric history, and an evaluation of the support systems available to them. PHARMACOTHERAPY. A growing list of agents that act at different points in viral replication has raised the hope that HIV might be permanently suppressed or actually eradicated from the body. These agents are divided into five major drug classes. Reverse transcriptase inhibitors (RTIs) interfere with the critical step during the HIV life cycle known as reverse transcription. There are two types of RTIs: nucleoside/nucleotide RTIs (NRTIs), which are faulty DNA building blocks, and non-nucleoside RTIs (NNRTIs), which bind to RT, interfering with its ability to convert the HIV RNA into HIV DNA. Protease inhibitors interfere with the protease enzyme that HIV uses to produce infectious viral particles. Fusion or entry inhibitors interfere with the virus’ ability to fuse with the cellular membrane, thereby blocking entry into the host cell. Integrase inhibitors block integrase, the enzyme HIV uses to integrate genetic material of the virus into its target host cell. Multidrug combination products combine drugs from more than one class into a single product. The most common of this class of drugs is the highly

active antiretroviral therapy (HAART). Table 21.5-7 lists the available agents in each of these categories. Table 21.5-7 Antiretroviral Agents The antiretroviral agents have many adverse effects. Of importance to psychiatrists is that protease inhibitors can increase levels of certain psychotropic drugs such as bupropion (Wellbutrin), meperidine (Demerol), various benzodiazepines, and selective serotonin reuptake inhibitors (SSRIs). Caution must be taken in prescribing psychotropic drugs to persons taking protease inhibitors.

PSYCHOTHERAPY. Major psychodynamic themes for patients infected with HIV involved self-blame, self-esteem, and issues regarding death. The entire range of psychotherapeutic approaches may be appropriate for patients with HIV-related disorders. Both individual and group therapy can be effective. Individual therapy may be either short term or long term and may be supportive, cognitive, behavioral, or psychodynamic. Group therapy techniques can range from psychodynamic to completely supportive in nature. Direct counseling regarding substance use and its potential adverse effects on health of the patient who is HIV infected is indicated. Specific treatments for particular substance-related disorders should be initiated if necessary for the total well-being of the patient. Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE) is an autoimmune disease that involves inflammation of multiple organ systems. The officially accepted diagnosis of SLE requires a patient to have four of 11 criteria that have been defined by the American Rheumatism Association. Between 5 and 50 percent of patients with SLE have mental symptoms at the initial presentation, and approximately 50 percent eventually show neuropsychiatric manifestations. The major symptoms are depression, insomnia, emotional lability, nervousness, and confusion. Treatment with steroids commonly induces further psychiatric complications, including mania and psychosis. Autoimmune Disorders Affecting Brain Neurotransmitters A group of autoimmune receptor-seeking disorders have been identified that cause an encephalitis that mimics schizophrenia. Among those is anti-NMDA(N-methyl Daspartate)-receptor encephalitis that causes dissociative symptoms, amnesia and vivid hallucinations. The disorder occurs mostly in women and was described in a memoir entitled Brain on Fire. There is no treatment although intravenous immunogloblins have proved useful. Recovery does occur but some patients might require prolonged intensive care. Endocrine Disorders Thyroid Disorders. Hyperthyroidism is characterized by confusion; anxiety; and an agitated, depressive syndrome. Patients may also complain of being easily fatigued and of feeling generally weak. Insomnia, weight loss despite increased appetite, tremulousness, palpitations, and increased perspiration are also common symptoms. Serious psychiatric symptoms include impairments in memory, orientation, and judgment; manic excitement; delusions; and hallucinations. In 1949, Irvin Asher named hypothyroidism “myxedema madness.” In its most severe form, hypothyroidism is characterized by paranoia, depression, hypomania, and hallucinations. Slowed thinking and delirium can also be symptoms. The physical symptoms include weight gain, a deep voice, thin and dry hair, loss of the lateral

eyebrow, facial puffiness, cold intolerance, and impaired hearing. Approximately 10 percent of all patients have residual neuropsychiatric symptoms after hormone replacement therapy. Parathyroid Disorders. Dysfunction of the parathyroid gland results in the abnormal regulation of calcium metabolism. Excessive secretion of parathyroid hormone causes hypercalcemia, which can result in delirium, personality changes, and apathy in 50 to 60 percent of patients and cognitive impairments in approximately 25 percent of patients. Neuromuscular excitability, which depends on proper calcium ion concentration, is reduced, and muscle weakness may appear. Hypocalcemia

can occur with hypoparathyroid disorders and can result in neuropsychiatric symptoms of delirium and personality changes. If the calcium level decreases gradually, clinicians may see the psychiatric symptoms without the characteristic tetany of hypocalcemia. Other symptoms of hypocalcemia are cataract formation, seizures, extrapyramidal symptoms, and increased intracranial pressure. Adrenal Disorders. Adrenal disorders disturb the normal secretion of hormones from the adrenal cortex and produce significant neurological and psychological changes. Patients with chronic adrenocortical insufficiency (Addison's disease), which is most frequently the result of adrenocortical atrophy or granulomatous invasion caused by tuberculous or fungal infection, exhibit mild mental symptoms, such as apathy, easy fatigability, irritability, and depression. Occasionally, confusion or psychotic reactions develop. Cortisone or one of its synthetic derivatives is effective in correcting such abnormalities. Excessive quantities of cortisol produced endogenously by an adrenocortical tumor or hyperplasia (Cushing's syndrome) lead to a secondary mood disorder, a syndrome of agitated depression, and often suicide. Decreased concentration and memory deficits may also be present. Psychotic reactions, with schizophrenia-like symptoms, are seen in a few patients. The administration of high doses of exogenous corticosteroids typically leads to a secondary mood disorder similar to mania. Severe depression can follow the termination of steroid therapy. Pituitary Disorders. Patients with total pituitary failure can exhibit psychiatric symptoms, particularly postpartum women who have hemorrhaged into the pituitary, a condition known as Sheehan's syndrome. Patients have a combination of symptoms, especially of thyroid and adrenal disorders, and can show virtually any psychiatric symptom. Metabolic Disorders A common cause of organic brain dysfunction, metabolic encephalopathy can produce alterations in mental processes, behavior, and neurological functions. The diagnosis should be considered whenever recent and rapid changes in behavior, thinking, and consciousness have occurred. The earliest signals are likely to be impairment of memory, particularly recent

memory, and impairment of orientation. Some patients become agitated, anxious, and hyperactive; others become quiet, withdrawn, and inactive. As metabolic encephalopathies progress, confusion or delirium gives way to decreased responsiveness; stupor; and, eventually, death. Hepatic Encephalopathy. Severe hepatic failure can result in hepatic encephalopathy, characterized by asterixis, hyperventilation, EEG abnormalities, and alterations in consciousness. The alterations in consciousness can range from apathy to drowsiness to coma. Associated psychiatric symptoms are changes in memory, general intellectual skills, and personality. Uremic Encephalopathy. Renal failure is associated with alterations in memory, orientation, and consciousness. Restlessness, crawling sensations on the limbs, muscle twitching, and persistent hiccups are associated symptoms. In young people with brief episodes of uremia, the neuropsychiatric symptoms tend to be reversible; in elderly people with long episodes of uremia, the neuropsychiatric symptoms can be irreversible. Hypoglycemic Encephalopathy. Hypoglycemic encephalopathy can be caused either by excessive endogenous production of insulin or by excessive exogenous insulin administration. The premonitory symptoms, which do not occur in every patient, include nausea, sweating, tachycardia, and feelings of hunger, apprehension, and restlessness. As the disorder progresses, disorientation, confusion, and hallucinations, as well as other neurological and medical symptoms, can develop. Stupor and coma can occur, and a residual and persistent dementia can sometimes be a serious neuropsychiatric sequela of the disorder. Diabetic Ketoacidosis. Diabetic ketoacidosis begins with feelings of weakness, easy fatigability, and listlessness and increasing polyuria and polydipsia. Headache and sometimes nausea and vomiting appear. Patients with diabetes mellitus have an increased likelihood of chronic dementia with general arteriosclerosis.

Acute Intermittent Porphyria. The porphyrias are disorders of heme biosynthesis that result in excessive accumulation of porphyrins. The triad of symptoms is acute, colicky abdominal pain; motor polyneuropathy; and psychosis. Acute intermittent porphyria is an autosomal dominant disorder that affects more women than men and has its onset between ages 20 and 50 years. The psychiatric symptoms include anxiety, insomnia, lability of mood, depression, and psychosis. Some studies have found that between 0.2 and 0.5 percent of chronic psychiatric patients may have undiagnosed porphyrias. Barbiturates precipitate or aggravate the attacks of acute porphyria, and the use of barbiturates for any reason is absolutely contraindicated in a person with acute intermittent porphyria and in anyone who has a relative with the disease. Nutritional Disorders

Niacin Deficiency. Dietary insufficiency of niacin (nicotinic acid) and its precursor tryptophan is associated with pellagra, a globally occurring nutritional deficiency disease seen in association with alcohol abuse, vegetarian diets, and extreme poverty and starvation. The neuropsychiatric symptoms of pellagra include apathy, irritability, insomnia, depression, and delirium; the medical symptoms include dermatitis, peripheral neuropathies, and diarrhea. The course of pellagra has traditionally been described as “five Ds”: dermatitis, diarrhea, delirium, dementia, and death. The response to treatment with nicotinic acid is rapid, but dementia from prolonged illness may improve only slowly and incompletely. Thiamine Deficiency. Thiamine (vitamin B1) deficiency leads to beriberi, characterized chiefly by cardiovascular and neurological changes, and to WernickeKorsakoff syndrome, which is most often associated with chronic alcohol abuse. Beriberi occurs primarily in Asia and in areas of famine and poverty. The psychiatric symptoms include apathy, depression, irritability, nervousness, and poor concentration; severe memory disorders can develop with prolonged deficiencies. Cobalamin Deficiency. Deficiencies in cobalamin (vitamin B12) arise because of the failure of the gastric mucosal cells to secrete a specific substance, intrinsic factor, required for the normal absorption of vitamin B12 in the ileum. The deficiency state is characterized by the development of a chronic macrocytic megaloblastic anemia (pernicious anemia) and by neurological manifestations resulting from degenerative changes in the peripheral nerves, the spinal cord, and the brain. Neurological changes are seen in approximately 80 percent of all patients. These changes are commonly associated with megaloblastic anemia, but they occasionally precede the onset of hematological abnormalities. Mental changes, such as apathy, depression, irritability, and moodiness, are common. In a few patients, encephalopathy and its associated delirium, delusions, hallucinations, dementia, and sometimes paranoid features are prominent and are sometimes called megaloblastic madness. The neurological manifestations of vitamin B12 deficiency can be rapidly and completely arrested by early and continued administration of parenteral vitamin therapy. Toxins Environmental toxins are becoming an increasingly serious threat to physical and mental health in contemporary society. Mercury. Mercury poisoning can be caused by either inorganic or organic mercury. Inorganic mercury poisoning results in the “mad hatter” syndrome (previously seen in workers in the hat industry who softened felt by putting it in their mouths), with depression, irritability, and psychosis. Associated neurological symptoms are headache, tremor, and weakness. Organic mercury poisoning can be caused by contaminated fish or grain and can result in depression, irritability, and cognitive impairment. Associated symptoms are sensory neuropathies, cerebellar ataxia, dysarthria, paresthesias, and

visual field defects. Mercury poisoning in pregnant women causes abnormal fetal development. No specific therapy is available, although chelation therapy with dimercaprol has been used in acute

poisoning. Lead. Lead poisoning occurs when the amount of lead ingested exceeds the body’s ability to eliminate it. It takes several months for toxic symptoms to appear. The signs and symptoms of lead poisoning depend on the level of lead in the blood. When lead reaches levels above 200 mg/L, symptoms of severe lead encephalopathy occur, with dizziness, clumsiness, ataxia, irritability, restlessness, headache, and insomnia. Later, an excited delirium occurs, with associated vomiting and visual disturbances, and progresses to convulsions, lethargy, and coma. Treatment of lead encephalopathy should be instituted as rapidly as possible, even without laboratory confirmation, because of the high mortality rate. The treatment of choice to facilitate lead excretion is intravenous administration of calcium disodium edetate (calcium disodium versenate) daily for 5 days. Manganese. Early manganese poisoning (sometimes called manganese madness) causes symptoms of headache, irritability, joint pains, and somnolence. An eventual picture appears of emotional lability, pathological laughter, nightmares, hallucinations, and compulsive and impulsive acts associated with periods of confusion and aggressiveness. Lesions involving the basal ganglia and pyramidal system result in gait impairment, rigidity, monotonous or whispering speech, tremors of the extremities and tongue, masked facies (manganese mask), micrographia, dystonia, dysarthria, and loss of equilibrium. The psychological effects tend to clear 3 or 4 months after the patient’s removal from the site of exposure, but neurological symptoms tend to remain stationary or to progress. No specific treatment exists for manganese poisoning, other than removal from the source of poisoning. The disorder is found in persons working in refining ore, brick workers, and those making steel casings. Arsenic. Chronic arsenic poisoning most commonly results from prolonged exposure to herbicides containing arsenic or from drinking water contaminated with arsenic. Arsenic is also used in the manufacture of silicon-based computer chips. Early signs of toxicity are skin pigmentation, GI complaints, renal and hepatic dysfunction, hair loss, and a characteristic garlic odor to the breath. Encephalopathy eventually occurs, with generalized sensory and motor loss. Chelation therapy with dimercaprol has been used successfully to treat arsenic poisoning. REFERENCES Boyd AD, Riba M. Depression and pancreatic cancer. J Natl Compr Canc Netw. 2007;5:113. Carrico AW, Riley ED, Johnson MO, Charlebois ED, Neilands TB, Remien RH, Lightfoot MA, Steward WT, Weinhardt LS, Kelly JA, Rotheram-Borus MJ, Morin SF, Chesney MA. Psychiatric risk factors for HIV disease progression: The role of inconsistent patterns of antiretroviral therapy utilization. J Acquir Immune Defic Syndr. 2011;56:146. Cahalan, S. Brain on Fire. Simon & Schuster, New York, 2013. Clare L, Whitaker CJ, Nelis SM. Self-concept in early stage dementia: Profile, course, correlates, predictors and implications for quality of life. Intern J Geriatric Psych. 2013;28:494.

06 - 21.6 Mild Cognitive Impairment

21.6 Mild Cognitive Impairment

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Impairment The past decade has seen the emergence of a new concept, mild cognitive impairment (MCI), which is defined as the presence of mild cognitive decline not warranting the diagnosis of dementia but with preserved basic activities of daily living. In the DSM-5, MCI is classified as mild neurocognitive disorder due to multiple etiologies or unspecified neurocognitive disorder. It will most likely receive more attention in future revisions of the DSM. DEFINITION

Although the term mild cognitive impairment has been in use for more than 25 years, it was suggested as a diagnostic category designed to fill the gap between cognitive changes associated with aging and cognitive impairment suggestive of dementia. The criteria proposed by the Mayo Clinic Alzheimer's Disease Research Center (MCADRC) are (1) memory complaint, preferably qualified by an informant; (2) objective memory impairment for age and education; (3) preserved general cognitive function; (4) intact activities of daily living; and (5) not demented (Table 21.6-1). However, at this time there are no international diagnostic criteria for MCI. Table 21.6-1 Mild Cognitive Impairment Original Criteria Historical Perspective The imprecise border between normal aging-related cognitive decline and dementia-related cognitive impairment has been described for several decades. Thus, in 1962, Kral introduced the terms benign senescent forgetfulness (forgetfulness for less important facts and awareness of problems) and malignant senescent forgetfulness (memory problems for recent events and lack of awareness). In 1986, the National Institutes of Mental Health (NIMH) recommended the term age associated memory impairment for age-related normal memory changes. In 1994, the International Psychogeriatrics Association presented the concept of age-associated cognitive decline, which described cognitive deficits including but not limited to memory impairment in the absence of dementia or other affecting cognitive conditions. Cognitive impairment no dementia was introduced in 1997 by the Canadian Study of Health and Aging to describe the presence of nondemented cognitive impairment regardless of the underlying process (neurological, psychiatric, medical). Several other classifications, including age-consistent memory impairment and late life forgetfulness, are defined on the bases of performance on various cognitive tests. The exact place of MCI in the psychiatric nosology will be challenging. Based on the current definition of MCI, functional impairment is an exclusion criterion for MCI, but the same "functional impairment" is one of the standard criteria for defining psychiatric disorders. Further developments in finding biological markers for MCI will probably contribute to a more solid conceptualization and, hopefully, treatment of patients with prodromal dementia (Table 21.6-2). Table 21.6-2 Terms Related to Mild Cognitive Impairment

EPIDEMIOLOGY AND ETIOLOGY OF MCI The recognition that Alzheimer's disease pathology may exist in the brain long before the presence of clinical symptoms led to the focus on preclinical stages, with the purpose of characterizing initial impairments that are associated with an increased risk of progression to Alzheimer's disease. The clinical expression of MCI can be viewed as a result of the interaction among several risk factors and several protective factors. The most significant risk factors are related to the different types of neurodegeneration witnessed in dementias. These are clinically expressed in different subtypes of MCI, especially those associated with amnesia. Other risk factors include the APOE4 allele status and cerebrovascular events in the form of either cerebrovascular accident or lacunar disease. The role of chronic exposure to high levels of cortisol, as seen in late life depression, is also hypothesized to increase the risk for cognitive impairment through hippocampal volume reduction. The notion of "brain reserve" suggests that effects of brain size and neuron density may be protective against dementia despite the presence of neurodegeneration (a larger number of neurons and a bigger brain volume would protect against

clinical manifestations of Alzheimer's disease despite the presence of neurodegeneration) (Fig. 21.6-1).

FIGURE 21.6-1 Outcome of clinical phenotypes of mild cognitive impairment (MCI) according to presumed etiology. AD, Alzheimer's disease; Depr, depression; DLB, dementia with Lewy bodies; FRD, frontotemporal dementia; VaD, vascular dementia. (Adapted with permission from Petersen RC, ed. Mild Cognitive Impairment: Aging to Alzheimer's Disease. New York: Oxford University Press; 2003.) CLINICAL PRESENTATION The clinical picture of MCI is a function of the criteria used to define it. Memory impairment is necessary but has been difficult to quantify. One measure has been objective loss of memory or other cognitive domain that is more than 1.5 standard deviations below the mean for individuals of similar age and education. Some have suggested subjective complaints of memory loss be used as a marker, but this runs the risk of many false-positive diagnoses. Assessment Neuropsychological Assessment. Most experts agree that earlier deficits are noted in episodic (vs. semantic) memory. There is no consensus among experts with regard to which memory tests and which cutoffs to use. There is a lack of norms, test scores do not have normal distributions, and test performance is influenced by multiple demographic characteristics. Several experts have proposed that a scale such as the delayed recall task from the Consortium to Establish a Registry for Alzheimer's Disease might be useful in detecting Alzheimer's disease in the earliest stages. Brief mental status instruments (e.g., the Mini-Mental State Examination) are relatively insensitive for the detection of memory problems in MCI. Biomarkers. Several markers of progression from MCI to Alzheimer's disease have been studies in the past decade. Among these, apolipoprotein E4 (ApoE4) allele carrier status has been one of the most prominent variables. For the amnestic MCI, ApoE4 has been shown to be a risk factor for a more rapid progression to Alzheimer's disease. Several CSF markers have also been identified as possible predictors of disease progression: Pathological low concentrations of Aβ42 (the 42 amino acid form of βamyloid) as well as pathological high concentrations of total tau (t-tau) and phospho tau (p-tau) may differentiate early Alzheimer's disease from normal aging. Locating alterations in the expression of proteins involved in the pathogenetic pathways of Alzheimer's disease (proteomic approach) is another approach used to help early detection of Alzheimer's disease. Several proteins (cystatin C, β-2 microglobulin, and BEGF polypeptides) have been detected through new techniques, and currently there are a number of proteins from both CSF and blood that are implicated in Alzheimer's disease pathology.

Genetics. Because MCI is regarded as the prodromal stage for several disorders (Alzheimer's disease, frontotemporal or vascular dementia), different genes are probably related to MCI. Four genes have been described in relationship with Alzheimer's disease: the amyloid precursor protein (APP) gene, presenilin-1 (PSEN1), presenilin-2 (PSEN2), and the apolipoprotein E (APOE) gene. Because the first three genes are involved in rare autosomal dominant forms of Alzheimer's disease, screening for each of these mutations will have very limited value for the diagnosis of MCI in the general population. The APOE gene, a common genetic risk factor for early as well as for late-onset Alzheimer's disease, has been studied more thoroughly in relationship to MCI, but the results have been inconsistent. Because the etiology of MCI is heterogenous, it is likely that a very large number of different genes underlie the pathology of MCI. Most of these genes are yet to be discovered. Neuroimaging. Advances in neuroimaging studies aim to develop measures allowing the differentiation between MCI and healthy aging as well as within MCI among subjects who will convert to Alzheimer's disease or will remain stable over time. Structural studies of volumetric MCI

showed early changes in the medial temporal structures, including neuronal atrophy, decreased synaptic density, and overall neuronal loss. Atrophy of the hippocampal volume and entorhinal cortex has been described in MCI. Atrophy of the hippocampal formation was also reported to predict the rate of progression from MCI to Alzheimer's disease. Three-dimensional modeling techniques have localized shape alteration and specific regions of atrophy within the hippocampus. Other methods such as tensor-based morphometry allow tracking brain changes in detail, quantifying tissue growth or atrophy throughout the brain and indicating the local rate at which tissue is being lost. Other innovations in neuroimaging include MR relaxometry, imaging of iron deposition, diffusion tensor imaging, and high-field MRI scanning. Perhaps the most promising development has been the advent of PET tracer compounds that visualize amyloid plaques and neurofibrillary tangles. These new compounds—Pittsburgh Compound B (carbon-11-PIB) and fluorine-18-FDDNP—track pathology changes in the preclinical stages of Alzheimer's disease. These specific tracers allow investigators to visualize the pathological process and are also used to monitor progression from MCI to Alzheimer's disease. However, the burden of β-amyloid plaques does not always correlate with the clinical stages because some MCI subjects can present with minimal burden similar to healthy control participants, but others have amyloid burden comparable to Alzheimer's disease participants. A single biomarker will probably be insufficient to identify incipient Alzheimer's disease. Thus, the combination of several markers further increases the accuracy of the prediction and will probably become the norm as described by recent studies (combination of decreased parietal rCBF and CSF biomarkers as Aβ42, t-tau, and p-tau) (Fig. 21.6-2).

FIGURE 21.6-2 Positron emission tomography images obtained with the amyloid-imaging agent Pittsburgh Compound-B ([carbon-11]-PIB) in a normal individual with mild cognitive impairment (MCI; center images) and a patient with mild Alzheimer's disease (AD) (far right). Some MCI patients have control-like levels of amyloid, some have Alzheimer's disease– like levels of amyloid, and some have intermediate levels. (Courtesy of William E. Klunk, M.D., University of Pittsburgh, Department of Psychiatry, Pittsburgh, PA. All rights retained.) Diagnostic Differential The Cognitive Continuum. The cognitive continuum describes the subtle pathway from age-related cognitive decline to MCI to dementia. Per this model, there is an overlap at both ends of MCI, which indicates that it can be quite challenging to identify the transition points (Figure 21.6-3). In practice, differentiating MCI from agerelated cognitive decline resides mainly on neuropsychological testing, showing a cognitive decline more severe for age and less education. The main differentiation between MCI and Alzheimer's disease resides in the lack of functional impairment in MCI. FIGURE 21.6-3 Cognitive continuum showing the overlap in the boundary between normal aging and the mild cognitive impairment and Alzheimer's disease. (Reprinted with permission from Petersen RC, ed. Mild Cognitive Impairment: Aging to Alzheimer's Disease. New York:

Oxford University Press, 2003.) COURSE AND PROGNOSIS The typical rate at which MCI patients progress to Alzheimer's disease is 10 to 15 percent per year and is associated with progressive loss of function. However, several studies have indicated that the diagnosis is not stable in both directions; patients can either convert to Alzheimer's disease or revert back to normal. This variability in course is related to the heterogeneous source of the subjects (clinical vs. community) as well as to the heterogeneous definition criteria used by different studies. Amnestic MCI has been associated with increased morbidity compared with reference subjects. TREATMENT There are no FDA-approved treatments for MCI at this time. MCI treatment involves adequate screening and

diagnosis. Ideally, MCI treatment would also include improvement of memory loss together with prevention of further cognitive decline to dementia. Cognitive training programs have been reported as mildly beneficial for compensating memory difficulties in MCI. Controlling for vascular risk factors (high blood pressure, hypercholesterolemia, diabetes mellitus) may be a benefit preventive method for those MCI cases underlying vascular pathology. Currently, sensitive tools (imaging techniques or biomarkers) are not available for MCI screening in the general population. In primary care setting, clinicians should maintain a high suspicion for subjective cognitive complaints and should corroborate these complaints with collateral information whenever possible. Also, identifying reversible causes of cognitive impairment (hypothyroidism, vitamin B12 deficiency, medication-induced cognitive impairment, depression) can further benefit some of the prodromal dementia MCI cases. Currently, there is no evidence for long-term efficacy of pharmacotherapies in reversing MCI. Several epidemiological studies indicated a reduced risk of dementia in persons taking antihypertensive medications, cholesterol-lowering drugs, antioxidants, and anti-inflammatory and estrogen therapy, but no randomized controlled trials verify these data. With regard to cognitive enhancers, as of 2007, there have been seven trials designed for amnestic MCI, with ambiguous results (Table 21.6-3). Most of these studies were confronted with several problems, including (1) obtaining homogeneous samples and identifying potential beneficiaries of treatment; (2) treating a wider population, which led to large percentages of negative responses and problematic side effects; and (3) translation of the MCI construct into multiple cultures and languages and using Alzheimer’s disease diagnosis as the primary outcome, given the variability of this diagnosis in different countries. Table 21.6-3 Treatment Trials for Mild Cognitive Impairment

Advances in MCI detection will be paramount for early detection and treatment of patients with Alzheimer’s disease; experts agree that disease-modifying treatments for Alzheimer’s disease will focus on cognitively intact individuals at increased risk. The field of identifying sensitive and specific biomarkers (biological and neuroimaging markers) will probably witness exponential development in the coming years. REFERENCES Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Berry-Kravis E. The apolipoprotein E epsilon4 allele and incident Alzheimer’s disease in persons with mild cognitive impairment. Neurocase. 2005;11:3. Andreescu C, Aizenstein HJ. Amnestic disorders and mild cognitive impairment. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1198. Birks J, Flicker L. Donepezil for mild cognitive impairment. Cochrane Database Syst Rev. 2006;3:CD006104. Breitner JC. Mild cognitive impairment and progression to dementia New findings. Neurology. 2014;82(4):e34–e35. Doody RS, Ferris SH, Salloway S, Meuser TM, Murthy AK, Li C, Goldman R: Identifying amnestic mild cognitive impairment in primary care. Clin Drug Invest. 2011;31:483. Edwards ER, Spira AP, Barnes DE, Yaffe K. Neuropsychiatric symptoms in mild cognitive impairment: Differences by subtype and progression to dementia. Int J Geriatr Psychiatry. 2009;24:716. Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, Walsh B, Cunningham C, Lawlor BA. Anxiety and behavioural disturbance as markers of prodromal Alzheimer’s disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry. 2011;26:166.

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disease. New York: Springer Science+Business Media; 2013:223. Pedersen KF, Larsen JP, Tysnes O-B, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: The Norwegian ParkWest Study. JAMA Neurol. 2013;70:580. Roberts JS, Karlawish JH, Uhlmann WR, Petersen RC, Green RC. Mild cognitive impairment in clinical care. Neurology. 2010;75:425. Rog LA, Fink JW. Mild cognitive impairment and normal aging. In: Ravdin LD, Katzen HL, eds. Handbook on the Neuropsychology of Aging and Dementia. New York: Springer Science+Business Media; 2013:239. Smith CN, Squire LR. Severe retrograde amnesia in amnestic mild cognitive impairment is related to damage in lateral temporal cortex. J Cogn Neurosci. 2013;January:171. Wang L, Goldstein FC, Veledar E, Levey AI, Lah JJ, Meltzer CC, Holder CA, Mao H. Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging. AJNR Am J Neuroradiol. 2009;30:893. Zola SM, Manzanares CM, Clopton P, Lah JJ, Levey AI. A behavioral task predicts conversion to mild cognitive impairment and Alzheimer’s disease. Am J Alzheimers Dis Other Demen. 2013;28:179.