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21.5 Neurocognitive and Other Disorders Due to a General Medical Condition

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anomaly (e.g., brain tumor), a neurotransmitter disturbance of unclear origin (e.g., schizophrenia), 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.

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