# CHAPTER 10. DELIRIUM, DEMENTIA, AND AMNESTIC AND OTHER COGNITIVE DISORDERS

ERIC D. CAINE, M.D. AND JEFFREY M. LYNESS, M.D.



Psychiatry is in the midst of a profound transformation, at once struggling to incorporate a dynamic understanding of neuroscience and molecular biology while maintaining a view of unique persons or individuals as the central focus of therapeutic intervention. To date it has been beyond the scope of knowledge to effectively integrate research data regarding individual differences with more abstract findings regarding fundamental aspects of brain development or aging-related neurodegeneration. Discovering the bases for the major neuropsychiatric diseases can be expected to provide powerful clues for defining the nature of how neurobiological processes are expressed as emotions, thoughts, or actions, or how life events and daily experiences alter and shape brain growth and development.

Since the late 1980s, a major conceptual transition has occurred in the way clinicians and researchers view the relation between mental disorders and brain function. For much of the past century psychiatry was trapped in an either-or dilemma—either a condition was viewed as a symptomatic manifestation of structural cerebral or systemic pathology (organic), or it was considered psychological or emotional in nature (functional). However, clinicians recognized that there are no behaviors that do not involve the brain, and that the transmission of culturally derived processes from individual to individual is influenced by each person's central nervous system (CNS). Behaviors defined by some cultures as abnormal may be mediated by normal neurophysiology; in contrast, patients with damaged brains may develop compensatory strategies reflective of CNS plasticity to ameliorate the effects of disordered neural systems. The same behavior (e.g., suicide) may reflect normal or abnormal physiology. For many diseases the CNS develops normally but acquires its dysfunction later in life whereas other diseases may reflect aberrant wiring patterns or connections that function in a neurochemically or

neurophysiologically normal fashion. Despite such complexity, clinicians often depended on a single criterion for defining organic disorders—either the detection of a structural lesion or, less often, the diagnosis of a known disease process; however, such an approach is no longer satisfactory.

Diagnostic decisions have depended largely on available technology. For more than a century gross postmortem examination and microscopic histopathological examination were the primary tools. Working in a tradition of clinical-pathological correlation, psychiatrists, neurologists, and others used a dichotomous approach to both diagnosis and classification—that is, a lesion was either present or absent. This approach proved heuristically limiting and became increasingly unrewarding. Indeed, histopathology is now no longer the gold standard for defining brain-based diseases. It was only marginally useful for psychiatry, and in the near future molecular biological methods will replace it for neurology. The advent of new technologies already has undermined the pseudocertainty of earlier years. Many patients with functional syndromes are found to have CNS abnormalities when studied with magnetic resonance imaging (MRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT). Should these syndromes be reclassified as organic? Most would argue that such changes would be premature because the pathophysiological significance of newer findings remains obscure. Such arguments also are pertinent to the entire question of organic versus functional.

The fourth edition of *Diagnostic and Statistical Manual of Mental Disorder* (DSM-IV) establishes a new approach to those questions. The categories of organic and functional have been abandoned. When a psychopathological syndrome is known to be a symptomatic manifestation of a systemic medical or cerebral disorder, it is designated as “due to . . .” (secondary), with a designation of the specific disease process. When it is considered to be an idiopathic psychiatric disturbance, it is designated primary. A clinician should follow a careful process of case reasoning before settling on the primary or secondary status of a disorder. To appropriately diagnose a patient as having an idiopathic (i.e., primary) condition, the clinician must necessarily exclude all definable, potentially etiological disease processes.

The clinician must exercise equal caution before diagnosing a disorder as secondary or symptomatic. To date there are no widely accepted guidelines for establishing probable causal relations between psychopathological conditions and detected cerebral abnormalities. Traditionally, such assignment of probable causality has been left to clinical judgment. DSM-IV outlines such guidelines; they have the effect of encouraging the clinician to undertake a thorough evaluation and to postulate causal connections conservatively.

## DEFINITION

The primary-secondary classification, like similar classifications, reflects the thinking of its time. The change in terminology in DSM-IV from *organic* to *due to* . . . is more than cosmetic in that it captures the conceptual shift away from structure and lesion and toward active disease process and etiology. The broad group of cognitive disorders includes dementia, delirium, amnestic disorder, and other syndromes in which disordered cognition caused by known (or presumed) disease entities is the central characteristic featuret (Table 10-1). Specific secondary syndromes are scattered through the nosology,

classified along with other phenomenologically similar clinical conditions (e.g., mood disorders due to general medical conditions are grouped among the mood disturbances). Such groupings are intended to foster differential diagnostic consideration; the changes in DSM-IV are intended to enhance rigorous clinical reasoning. Use of more specific designations (e.g., mood disorder due to thyroid deficiency, with major depressive-like episode) strengthens diagnostic specificity when contrasted to the previously used organic mood disorder and lays the foundation for more meaningful comparative research.

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| Delirium |
| Delirium due to a general medical condition |
| Substance-induced delirium |
| Delirium due to multiple etiologies |
| Delirium not otherwise specified |
| Dementia |
| Dementia of the Alzheimer's type |
| Vascular dementia |
| Dementia due to other general medical conditions |
| Dementia due to HIV disease |
| Dementia due to head trauma |
| Dementia due to Parkinson's disease |
| Dementia due to Huntington's disease |
| Dementia due to Pick's disease |
| Dementia due to Creutzfeldt-Jakob disease |
| Dementia due to other general medical conditions |
| Substance-induced persisting dementia |
| Dementia due to multiple etiologies |
| Dementia not otherwise specified |
| Amnestic disorders |
| Amnestic disorder due to a general medical condition |
| Substance-induced persisting amnestic disorder |
| Amnestic disorder not otherwise specified |
| Cognitive disorder not otherwise specified |

**Table 10-1** DSM-IV Cognitive Disorders

Throughout this chapter the term “neuropsychiatry” is used in reference to the field of medicine that considers the brain bases of mental disorders. In the United Kingdom this field is sometimes called organic psychiatry. At one time nearly all of psychiatry was neuropsychiatry; at another time, few would have chosen that label. Considering the brain substrates of behavior necessarily forces clinicians and researchers also to recognize the experiential, psychological, social, and cultural aspects of the patients and the problems they encounter.

## HISTORY

The development of neuropsychiatry and the growth of general psychiatry coincided with competition and ultimately cooperation between public psychiatric asylums (now called hospitals or centers) and clinical practice in universities and private offices. Different ideologies or dogmas developed, depending on whether the clinician was seeing principally institutionalized psychotic patients, for whom there was little hope for improvement or recovery, or ambulatory patients, whose apparent psychological accessibility gave rise to therapeutic optimism. Additionally, psychiatrists in the asylums (often called alienists) had different needs than the nerve doctors or neurointernists who saw the walking wounded in their offices.

Table 10-2 presents a brief categorization of historical periods in neuropsychiatry. It is probably not presumptuous to state that Wilhelm Griesinger (1817–1868) created neuropsychiatry with the publication of his book in 1845, crafted after practicing 2 years in Winenthal, one of the leading German asylums. An advocate of physiological medicine, Griesinger attempted to steer German medical practice away from both the romantic and somatic schools of that time. He asserted that psychiatry was part of medicine and that “psychological diseases are diseases of the brain.” He also advocated knowing one's

patients well, understanding their life course, and appreciating how their mental disease affected their overall functioning. He advanced a specific notion of the ego that attempted to explain all disease under a single conceptual view based on a gradual pathological erosion of ego integrity. He supported the idea of careful neuropathological observation, although he never pursued such work in the later fashion of Theodor H. Meynert, Karl Wernicke, or Alois Alzheimer.

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| 1845–1865 | Griesinger—Integration I |
| 1865–1900 | Neuropathological and descriptive psychiatry |
| 1900–1930 | Gradual transition I |
| 1930–1950 | Ferment |
| 1950–1965 | Psychodynamic era (United States) |
| 1965–present | Gradual transition II |
| The future | Integration II |

**Table 10-2** Historical Periods in Neuropsychiatry

Despite Griesinger's attempted integration, many of his notions now seem simplistic or misleading, especially the idea that all mental illnesses reflected one basic pathological process that could be divided into stages. The first of Griesinger's disease stages involved an assault on the ego by the basic disease, although no frank pathological disruption was apparent. In the second and third stages, ego disintegration was completed and permanent brain changes took place. Griesinger believed that therapeutic intervention would be successful only during the first stage. Griesinger and his contemporaries made no particular distinction between psychiatric and neurological problems, and patients with progressive neurological diseases were seen in asylums like Winenthal. He proposed joint psychiatry and neurology clinics, and founded one in Berlin in 1861. Most importantly he catalyzed the development of university neuropsychiatry in contrast to the asylum psychiatry that was prevalent in his day, and thus provided the means for developing academic, research-based approaches to questions that had largely been outside rigorous medical scrutiny.

Meynert (1833–1893), the next major player on the neuropsychiatric scene, steered away from Griesinger's integrative center toward an extreme of neuropathological determinism. Meynert's 1874 book, titled *Psychiatry: Diseases of the Forebrain*, largely dealt with neuroanatomy. He is probably best remembered for his histopathological studies and has deservedly been called a pioneer of neuropsychiatric pathophysiology. Meynert also consolidated within universities what proved to be both a sterile theoretical position and a form of clinical psychiatry that had little benefit for either patients in the asylum or the walking wounded. Perhaps unwittingly, Meynert and his intellectual colleagues placed neuropsychiatry in a position where it would decline. It was presumptuous to believe that all clinically significant behavioral disturbances had a demonstrable cerebral substrate, especially given available laboratory techniques. Such work took place in a context of minimal understanding of the basic aspects of neuronal or regional cerebral functioning. It was ironic that the driving investigative force, a search for pathologically defined brain abnormalities, was to become a basis for undoing the field. Psychiatry in general and neuropsychiatry in particular have been plagued by a sense of intellectual exclusivity—the

either-or dilemma—in their intellectual conceptions. This sense of exclusivity and the related tendency to decry integrative (multidetermined) theoretical approaches may have reflected the ultimate conceptual complexity of the research and clinical tasks that have confronted those who would understand the cerebral bases of behavior and mental disorders: “the brain we are studying is more complex than the brain that is studying it.”

In the context of these limitations of neuropsychiatry, two fundamentally different paths emerged. The first was exemplified by the work of Emil Kraepelin (1856–1926). Although Kraepelin supported the neuropathological work of Alzheimer, he spent considerable effort developing a rigorous clinical classification of psychiatric disorders, particularly those observed in asylum settings. The classification was largely atheoretical, based as it was on form and course. Kraepelin hoped that clinical description and classification would ultimately lead to pathological correlation, a hope that has yet to be realized fully. The second path was developed by nerve doctors, neurointernists who saw their patients in offices or on the wards of neurological hospitals. Jean Martin Charcot (1825–1893) and Sigmund Freud (1856–1939) were notable among those practitioners. The idea of looking at an individual's development in the context of early life experience did not originate with Freud (Griesinger had also advocated it), but Freud pushed farthest the notion of defining the meaning of particular behaviors in terms of real and imagined life events. The different paths blazed by Freud, Kraepelin, and Meynert coexisted during the early decades of the twentieth century, with no one route of investigation clearly predominant. Clinical-pathological correlation had its greatest triumphs with the recognition of the causes of general paresis and pellagra. However, the large asylums remained full, and there were no specific therapies for clinicians to use.

In the United States, by contrast, the period from 1930 to 1950 was a time of great ferment and change, with an examination of new ideas and therapies. Shortly before World War II clinicians experimented with a variety of somatic interventions and opined about the cerebral bases of the major psychiatric disorders. New treatments, including barbiturate coma, insulin shock, and the convulsive therapies, were developed. During this time of novel therapeutics, clinicians undertook what seemed a logical step to many—ablative neurosurgical intervention, ultimately dubbed psychosurgery. Although it was based on poorly substantiated notions of cerebral functions and how they went awry in the major psychiatric disorders, frontal lobotomy spread rapidly in the United States following World War II, fueled by a desire to empty large state mental hospitals and reduce public expenditures for patients with chronic mental disorders. Psychosurgery offered the prospect of instituting a definitive medical procedure that either cured or markedly improved previously intractable syndromes. However, psychosurgery and its practitioners failed to fulfill their promises and neuropsychiatry eventually became a term of opprobrium. By the mid-1950s brain-oriented views of behavior were widely considered to offer few clinically or theoretically fruitful insights, and brain-oriented psychiatrists were seen as useless or even clinically harmful to those they treated. Juxtaposed with the 1930s' plunge into organic psychiatry and its therapies was the growth of psychoanalysis, sparked by revolutionary theories brought from Europe by analysts fleeing Adolf Hitler. Young neuropsychiatrists, neurologists, and neuroscientists proved a receptive audience for these ideas, as they discovered far greater explanatory power in the notions of Freud than in those of Charles Sherrington and the doctrine of nerve transmission. Enthusiasts found analytic insights filling unmet needs: Freud's theories and techniques supplied both tools for data

collection through the free-associative interview and a coherent system to organize these findings. More importantly, these techniques directed specific interventions and provided the physician with something to do beyond watching impaired patients remain unchanged or become progressively worse.

Stanley Cobb (1887–1968) was among the leaders in the attempt to integrate psychiatry and neurology. Cobb trained in neuropathology and taught the basic neuropathology course at Harvard Medical School for several generations. A student of Adolf Meyer, he espoused a dynamic life course view. Although he maintained an appreciation for neuropathology, he moved away from a primary interest in cerebral circulation to a consideration of psychiatric disorders during the late 1920s and the 1930s. Cobb developed a conceptual pyramid as an integrative device to illustrate his views, deliberately leaving a gray, uncharted zone between pathology and clinical psychiatry. Despite subsequent advances in neuroscience, the uncharted zone seems no less opaque now than 60 years ago, when Cobb first published the conceptual pyramid in his textbooks.

The years immediately after World War II were a time of rapid change, away from neuropathology-based psychiatry and toward psychodynamic and psychoanalytic psychiatry. The growth of psychiatry departments and medical schools was spurred by federal initiative, as was the deinstitutionalization of the seriously ill. Economic motives contributed to the latter, but more important was the sense that a therapeutic triumph might be at hand. This sense was associated with the optimism following World War II of psychiatrists and psychiatrists-to-be (often physicians from other disciplines who were assigned to wartime psychiatry services), coupled with the hope for the successful use of psychoanalysis in a wide variety of disorders and the development, during the 1950s, of a more specific psychopharmacology. Notably, psychopharmacology did not reflect a greater degree of neuroscientific understanding; rather, serendipity, clinical acumen, and innovative thinking served as guiding beacons. Later developments of new compounds did result from attempts at pharmacological modeling. Indeed, more recent understandings of CNS function were catalyzed by having specific agents that could reliably alter brain activity. Central to this activity were industry-sponsored initiatives to discover and develop novel pharmacotherapeutic medications.

Formal psychiatric classification and nomenclature evolved during the post-World War II era. Prior to the adoption of the first edition of DSM (DSM-I) in 1952, psychiatric hospitals used the *Statistical Manual for the Use of Hospitals for Mental Disease,* first published under a slightly different title in 1918. Nearly all the categories in the manual were used for classifying patients with brain-related mental disturbances. As noted in DSM, that approach proved suitable for only about 10 percent of the cases seen by the Armed Forces during World War II. In contrast to the *Statistical Manual for the Use of Hospitals for Mental Disease*, DSM outlined two broad categories, one for disorders caused by or associated with impairment of brain tissue function (divided into acute and chronic), and the second for those of psychogenic origin without clearly defined physical cause or structural change in the brain. The brain disorder section classified conditions by duration and defined etiology (e.g., infection, intoxication, and tumor) with no attention to clinical phenomena whereas the psychogenic section began the move toward a more clinically specific categorization. For the latter, difficulties adjusting to internal and external stresses were the key pathogenic factors. Thus, a psychological theory officially supplanted the dominant brain view of earlier classification manuals. Despite the change in dominant explanatory

theory, DSM also maintained and further codified an either-or philosophy set forth by the earlier post-Griesinger neuropsychiatrists.

A similar stance was taken in the second edition of DSM (DSM-II), with a separation of organic brain syndromes from psychoses not attributed to physical conditions listed previously. Brain syndromes were said to result from diffuse impairment of brain tissue and to be manifested by the following symptoms: impairment of orientation, memory, all intellectual functions (e.g., comprehension and calculation), and judgment, as well as lability and shallowness of affect. The organic brain syndromes were divided into psychotic and nonpsychotic conditions, the former also including senile and presenile dementia, depending solely on the severity of functional impairment. Beyond that crude separation, there were no specifying clinical features; further classification depended on defining a cause. *Acute* and *chronic* were indicated as diagnostic subcodes. Psychodynamic psychiatry was not successful in treating the more seriously impaired residents of the state hospitals, and often was found wanting among ambulatory populations. Competing approaches sprang up that claimed similar or greater effectiveness. Overall, it has been difficult to definitively demonstrate treatment success when using psychotherapeutic modalities, although recent efforts at treatment evaluation have proved both more enlightening and more promising. A neurochemically oriented biological psychiatry took hold and became pre-eminent in the research laboratory, if not always in the clinic setting. However, there has been no successful jump from synapse to behavior, integrating understanding anew. This dearth of explanation has made a fertile soil for the reemergence of neuropsychiatry.

## COMPARATIVE NOSOLOGY

**DSM-III and DSM-III-R** The third edition of DSM (DSM-III), published in 1980, and the 1987 revised third edition (DSM-III-R) moved to discard the theoretical underpinnings based on stress-related psychological reactions and emphasized phenomenology as part of an innovative multiaxial system of classification. Nonetheless, the organic versus nonorganic dichotomy was maintained. Organic mental disorders were clearer in their clinical typology, with a greater array of subtypes and causes, related either to Axis III physical disorders or conditions or to use of psychoactive substances. Importantly, categories for mood, personality, anxiety, and hallucinatory and delusional disorders were added. These changes were made in an effort to increase recognition of clinical variations, but they lacked sufficient descriptive detail to allow reliable comparisons with idiopathic Axis I syndromes. Unfortunately, like DSM-I and DSM-II, DSM-III provided no guidelines or discussion on the question of causal connection between systemic medical or cerebral diseases and secondary psychiatric manifestations. Thus, there has been no consideration of the clinical reliability of the organic designation or of its validity.

**Scientific Developments** Since the 1970s a period of transition characterized by the absence of a dominant theoretical view within psychiatry has been under way. Scientific developments outside the field have profoundly shifted the direction of psychiatric thought and have come largely from behavioral neurology, clinical neuropsychology, and basic laboratory neuroscience. Challenged by the rehabilitative needs of many patients returning from World War II with focal cerebral lesions, a small number of neurologists and quantitative psychologists began to study the effects of those injuries just as

psychiatrists were shifting their attention away from cerebral processes. This work quickly expanded to include patients with vascular lesions. By the late 1960s behavioral neurologists and clinical neuropsychologists were recognized specialists, although few in number, and a growing literature examined the intellectual and behavioral consequences of specific regional cerebral lesions. These writings stimulated a modern resurgence of the clinical-pathological correlative tradition first developed during the late 1800s. Since the late 1980s psychiatric researchers have drawn increasingly from the lessons of focal lesion models.

Simultaneously, basic laboratory neuroscience burgeoned, with important findings reported at a fast pace in recent years. Researchers have moved from a focus on synapses and neurons to subneuronal molecular biological processes. Investigative techniques have changed extremely quickly, facilitating the detection of variations in complex neurobiological systems while outstripping the ability to define the terms *normal* and *abnormal*.

Even as psychiatric researchers studied focal lesion syndromes with greater enthusiasm, the shortcomings of those models became more apparent. Most importantly, they involve cerebral substrates distinctly different from those of the major idiopathic psychiatric syndromes. Whereas strokes reflect vascular anatomy, major psychopathology is based on dysfunction in interacting and widespread neurochemical systems. Many clinical psychiatric disorders reflect long-term (perhaps developmental) abnormalities that affect psychological growth and interpersonal events across the life span. Focal cerebral lesions on the other hand are acquired later in life in the context of a developmentally intact CNS; thus, analogies must be drawn with caution.

Psychiatric researchers face another, more daunting obstacle when considering the brain bases of mental disorders. Since the 1970s many have chosen to compare specific diagnoses with putative CNS alterations. The exclusive use of categorical diagnoses, while beneficial for enhancing clinical rigor, has yet to prove rewarding when applied to diagnosis-brain correlative research paradigms. Although empirically defined clinical syndromes form the bedrock of modern psychopharmacology, they may not be amenable to fundamental neurobiological characterization.

The historic lessons of neuropsychiatry include the realization that a defined or unified etiology may be associated with a striking diversity of clinical presentation (e.g., general paresis and Huntington's disease); conversely, specific syndromes are often the manifestation of heterogeneous etiologies. Here again, maintenance of a rigid either-or view is likely to prove disappointing. Rather, future researchers will be required to understand how experiences in the midst of normal development permanently change the brain. Too often neuropsychiatry has viewed the universe along the trajectory of brain to behavior. It will be just as important to understand it from behavior to brain and back again. Psychiatry as a broad field, and neuropsychiatry in particular, must address an array of key questions regarding brain-behavior and behavior-brain relationships.

1. How do developmental abnormalities that occur in utero or in the early years of life lead to later emerging psychopathology? What are the genetic and environmental causes of these defects, and

what are their molecular biological modes of expression?
2. How does environment and life experience change brain structure and function? In essence, what are the mechanisms of brain plasticity? How do normative and abnormally stressful life events lead to permanent changes in neural function?
3. How is brain and organism homeostasis maintained or lost? What are the neural underpinnings of cyclical or episodic changes in behavioral, emotional, and cognitive functioning?
4. What are the genetic, molecular, and environmental factors associated with brain aging and normative cognitive decline, and neurodegenerative diseases?

The limits of neuroscientific inquiry need to be recognized. Neuroscience will not improve the interviewing skills of an individual psychiatrist; moreover, it will be many years or decades before there is a clear understanding of the neural bases for individual differences: When the field progresses to the point where clinicians and scientists can merge an appreciation of a person's life story with knowledge regarding laws of the nervous system, it will finally reach a level of true integration.

**DSM-IV** The change in terminology in DSM-IV from *organic* to *due to* represents more than a simple semantic alteration—it emphasizes the need to define etiology, not site or structure. The term "*organic*", as used for many years pointed to defined pathological lesions and was contrasted with the term "*functional*" or physiological abnormalities that could not be detected by existing laboratory procedures. In the absence of sensitive and specific diagnostic laboratory tests, descriptive laboratory technology was often misapplied, giving a false impression of diagnostic validity. Similarly, the presence of a definable abnormality was considered sufficient to establish an organic diagnosis even though no standards were available for setting a threshold of evidence or data needed to attribute the cause of a symptom to an observed lesion.

DSM-IV takes a conservative approach to the problem. Establishing a secondary diagnosis should, whenever feasible, follow a chain of reasoning that etiologically connects a psychopathological syndrome with a systemic medical or primary cerebral disorder. The coexistence of Axis I and Axis III diagnoses in an individual case is not sufficient to infer a causal relationship, even when an apparent association or correlation is present. To more confidently determine whether an association is causal, the clinician should attempt to define the strength (relative risk), consistency of form, specificity, coherence of association, and temporal relation of clinical manifestations to the proposed disease process. Defining each attribute may not be feasible for all disorders or in every case, but it does provide stronger ground for advancing an etiological link. When insufficient data are available to establish a causal relation, it is preferable to provide unlinked Axis I and Axis III diagnoses.

It is notable that the 10th revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) maintained "organic" as a superordinate category. Although many specific examples of syndromic diagnostic criteria are similar to those in DSM-IV, ICD-10 retained the approach favored by earlier editions of the DSM. Where DSM-IV strives to highlight steps necessary for establishing a primary general medical diagnosis, ICD-10 states: "Rather, the clinical manifestations resemble, or are identical with, those of disorders not regarded as 'organic' in the specific sense restricted to this block of the classification. Their inclusion here is based on the hypothesis that they are

directly caused by cerebral disease or dysfunction rather than resulting from either a fortuitous association. . . or a psychological reaction to its symptoms. . .”

## DIAGNOSIS

Thorough clinical evaluation forms the basis for diagnosing secondary disorders. Beyond a detailed personal history and mental status examination, the clinician often must depend on supplementary laboratory evaluation, including such procedures as cerebral imaging, neuropsychological testing, and electroencephalography (EEG). Four steps form the basis for establishing a secondary (“due to . . .”) diagnosis with greater confidence: (1) definition of the specific psychopathological syndrome, (2) delineation of other manifestations of the primary disorder, (3) demonstration of active cerebral or systemic disease, and (4) demonstration of an elevated prevalence between the proposed etiological disorder and the described psychopathological picture. These steps may not always occur sequentially, as both syndrome and disease may be recognized.

**Definition of the Specific Psychopathological Syndrome** It is essential to describe the clinical disorder as precisely as possible. Subtyping should be undertaken when feasible, particularly with the specification of target symptoms for treatment. Use of broader or not otherwise specified terminology is available for less phenomenologically specific cases. Ideally, the clinician seeks to establish etiological relationships between definable disease processes and specific clinical presentations. The multiple presentations of general paresis, however, underscore that one pathogenic agent may cause multiple syndromic forms.

Patients with many secondary psychiatric disturbances present with symptoms that are atypical of primary (idiopathic) psychiatric disorders. Other clinical features, such as older age at onset, may serve to raise the index of suspicion. Syndrome definition involves severity as well as form. Severity implies a continuum, and the application of a diagnosis implies that the disorder has exceeded a threshold of severity. For example, although behavioral changes often arise following a cerebral lesion, a categorical diagnosis is not warranted when symptoms have not had a measurable impact on a person's functional integrity. Researchers may wish to study mildly symptomatic phenomena, but clinicians typically reserve diagnoses for conditions that cause substantially disordered behaviors, those interfering with the patient's daily life and personal well-being.

**Delineation of Other Manifestations of the Primary Disorder** Secondary psychopathological syndromes rarely occur alone but typically keep company with other symptoms and signs of the primary systemic or cerebral disorder. Thus, it is essential to define those cognitive, neuropsychological, peripheral, or other clinically ascertained manifestations of the disease process. For example, human immunodeficiency virus (HIV)-induced manic symptoms typically are accompanied by signs of testable cognitive impairment whereas depression due to Huntington's disease can be diagnosed with confidence only in the setting of a defined movement disorder. Identifying co-occurring manifestation provides an overall clinical context for more confidently establishing a secondary diagnosis.

**Demonstration of Active Cerebral or Systemic Disease** The clinician should seek nonbehavioral confirmation of the primary disease process. Such confirmation typically involves laboratory testing, including the full array of medical diagnostic procedures. One must be cautious, however, in the interpretation of many tests. An example is the use of cerebral imaging in psychiatric patients. Detection of a structural abnormality on computed tomography (CT) or MRI is not equivalent to demonstrating active cerebral disease because such imaging studies provide static (i.e., nonphysiological, nonfunctional) information in most applications. Much remains unknown regarding the link between MRI findings, definable cerebral pathology, and specific pathophysiologies or diseases.

**Elevated Prevalence Rate Between Proposed Etiological Disorder and Described Pathological Picture** This guideline cannot always be fulfilled, but argues for utilizing data-based conclusions that can be applied to clinical practice. Simply recording that a change in behavior occurs after the emergence of a particular cerebral disorder, for example, is insufficient proof. A specific syndrome should occur with a prevalence in association with an etiological disorder that is above the base rate in the general population.

Many clinicians recommend as the principal criterion for establishing causality the demonstration of a close temporal association of onset and course of the primary disorder and the secondary psychiatric syndrome. Although frequently useful, this criterion is not always applicable. For example, symptomatic psychosis due to epilepsy may gradually emerge 10 to 15 years after the onset of seizures. Conversely, psychiatric symptoms and signs may be the first clues to a systemic or cerebral disease, and detection of the primary pathological process may follow the emergence of psychiatric symptoms by months or longer. Many secondary psychiatric conditions also may persist after the primary disease process has resolved; examples are the secondary conditions consequent on thyroid deficiency, long-term alcohol use, or long-term exposure to neurotoxic compounds. Secondary syndromes may remit quickly, slowly, or incompletely, depending on the specific disease and whether lasting cerebral changes are present. Also, secondary syndromes may be amenable to symptomatic treatment even while the primary disorder remains without a cure.

ICD-10 recommends four criteria for classifying a syndrome as organic: (1) evidence of cerebral disease, damage, or dysfunction, or of systemic physical disease, known to be associated with one of the listed syndromes; (2) a temporal relationship (weeks or a few months) between the development of the underlying disease and the onset of the mental syndrome; (3) recovery from the mental disorder following removal or improvement of the underlying presumed cause; and (4) absence of evidence to suggest an alternative cause of the mental syndrome (such as a strong family history or precipitating stress).

ICD-10 also lists conditions known to increase the relative risk for the syndromes classified here, including epilepsy; limbic encephalitis; Huntington's disease; head trauma; brain neoplasms; extracranial neoplasms with remote CNS effects (especially carcinoma of the pancreas); vascular cerebral disease, lesions, or malformations; lupus erythematosus and other collagen diseases; endocrine disease (especially hypothyroidism and hyperthyroidism, Cushing's disease); metabolic disorders (e.g., hypoglycemia, porphyria, hypoxia); tropical infectious and parasitic diseases (e.g., trypanosomiasis);

toxic effects of nonpsychotropic drugs (propranolol [Inderal], levodopa [Dopar], methyldopa [Aldomet], steroids, and antihypertensive and antimalarial agents).

Ultimately the clinician must make an informed judgment as to whether the psychiatric condition is primary or secondary. Prevalence data, for example, reflect group trends whereas the clinician has to make a decision regarding an individual. Two approaches are available. The clinical decision is relatively uncomplicated if a previously demonstrated elevated prevalence links a specific syndrome with a specific etiology, in the presence of additional supporting clinical features and consistent laboratory tests. Probabilistic reasoning in such cases leads to the conclusion that there is a cause-and-effect relation. A temporal association, when meaningfully present, further confirms the connection.

When a clinical research data base is less well established, however, it becomes even more critical to document rigorous clinical reasoning, in effect demonstrating how the detected historical, clinical, and laboratory features are not consistent with what is known about idiopathic psychiatric conditions. Again, establishing the causal connection should reflect the clinician's effort to undertake conscientious probabilistic case reasoning. Attribution of a secondary designation implies a link that is more probable than not: a standard that exceeds 50 percent is recommended, although absolute certainty may be possible. Such a standard does not require that the systemic medical or primary cerebral disease be the sole factor contributing to symptom expression; rather, *due to . . .* connotes a predominant pathogenic role. When causal probability is considered less certain (i.e., possible but not probable), the clinician should not define a syndrome as secondary in nature.

Diagnostic decisions based on incomplete data will be inevitable, and thoughtful clinical judgment remains the abiding rule. *Due to . . .* should be used conservatively; attribution of cause invites a careful consideration of the factors that contribute to disease formation. When doubt remains, the provision of a primary (idiopathic) psychiatric diagnosis will best serve the interests of the patient and avoid the premature closure of clinical evaluation.

**Neuropsychiatric Assessment** Neuropsychiatric assessment follows the principles of all comprehensive clinical evaluations: it is based on thorough acquisition of the current and past medical history, family history, developmental and social history, and a review of personal habits. The neuropsychiatric clinician seeks to integrate the data on unique individual development, the signs and symptoms of disease, and an understanding of behavior-brain relationships into a meaningful appraisal of functional integrity.

Clinical reasoning should entail a time-oriented view, with the clinician noting how the patient has progressed or failed to develop across his or her life course. The temporal perspective is buttressed by an understanding of normative development as well as by an appreciation of the natural history of disease processes. In particular, the clinician should be mindful of the unique characteristics of primary cerebral disorders, whether inborn, acquired early in life, or of later onset. Fundamental to neuropsychiatric evaluation, diagnosis, and prognosis is an understanding of disease evolution at psychological and neurobiological levels of analysis. Frequently the clinician must tolerate the uncertainty of not knowing

(in an absolute sense) the mechanisms by which brain diseases cause behavioral problems; the clinician then has the task of developing practical and effective solutions to problems that may not have specific scientific answers. Despite having a recognized pathological basis, most neuropsychiatric disorders do not have specific cures and continue to require empirical, symptomatic treatment approaches.

Clinicians repeatedly face a dual dilemma: etiological specificity often is related to variable clinical expression (e.g., general paresis and Huntington's disease). There is no biological law such as “one pathogen, one clinical presentation.” Clinical variability is the rule rather than the exception. Conversely, there are relatively few final common pathways for the expression of a wide variety of disease processes. These pathways include (1) alterations in arousal, attention, and concentration; (2) alterations in affective state, including both the expression of emotion and the feeling of mood; (3) alterations in perception, including ideational or physical and internal or external; (4) alterations in intellectual function (such as memory, language, or the organization of thought processes); (5) alterations in personality; and (6) alterations in motor function. Thus, behavioral abnormalities tend to be nonspecific, and despite substantial evidence from behavioral neurology that focal lesions may lead to distinctive patterns of intellectual deficit, there are insufficient data to confidently support such assertions for major psychopathological syndromes. Moreover, idiopathic or primary psychiatric disorders may mimic symptomatic psychopathological conditions that are secondary to specific systemic medical or cerebral disease processes and vice versa. What confounds the situation is that there has been insufficient research to establish how often cerebral lesions lead to discrete psychopathological syndromes or specifically how any defined psychopathological disorder is related to a particular localized cerebral abnormality.

Thus, the clinician must use an empirical method, based on careful clinical reasoning, that allows the development of a preliminary diagnosis and an initial treatment plan. The clinician should specify in advance what possible therapeutic benefits might be derived and should understand how the natural history of the disorder will unfold if proposed treatment options prove ineffective. The clinician should also be ready to undertake further evaluation if an unanticipated outcome arises. By establishing a future-oriented or outcome-oriented clinical perspective, the clinician can reduce the degree of uncertainty and establish a structural approach for systematically and self-critically scrutinizing treatment interventions.

**Neuropsychiatric Case Reasoning** The approach to neuropsychiatric case reasoning required for such formulation and planning entails blending the disparate traditions that developed in psychiatry in the past century. It draws from Meynert and John Hughlings Jackson (1835-1911), as well as from the behavioral neurologists of recent decades, an appreciation of brain-behavior and behavior-brain relations, with an attempt to understand the laws that govern the CNS. Such a pathobiological method, through lesion location and an appreciation of probabilistic generalities about brain function and neuropathology, in effect argues that all nervous systems are created equal. It benefits from a thoroughly documented array of case studies that seek to define the specific behavioral expression of focal cerebral lesions. It suffers from the fact that nervous systems are not identical and that personal circumstances powerfully influence the expression of disease. Nonetheless, it has taught clinicians much about what to assess and expect when dealing with disordered brain function.

The second approach to case reasoning is derived from the Kraepelinian tradition that continues to be expressed in DSM-IV. This method argues for the precise elaboration of symptoms and signs, the definition of specific syndromes, the identification of target symptoms amenable to therapeutic intervention, and the use of diagnoses for prognostic purposes. The strengths of such an approach lie in the rigorous case definition based on thorough observation and data collection, with the derived ability to generalize from one case to another. Shortcomings, akin to the problems with lesion localization, include the substantial degree of variability that exists within the boundaries of stereotypic diagnostic descriptions and the difficult-to-quantify influences of personal life circumstances.

The third method of case reasoning evolved from dynamic psychiatry and recognizes the individual as having unique personal and developmental attributes that are expressed throughout the course of life. The clinician using this method of case reasoning seeks to understand meaning as well as event and to appreciate disease process in the patient's broader social and cultural context. The neuropsychiatric clinician must view illness in all its complexity.

The different modes of case reasoning are brought together for clinical purposes through understanding how psychological meaning, symptoms, and disease process and socially defined aspects of illness each affects the patient's ability to function autonomously. Although function is not a direct measure of pathology or disease process, assessing how each person has undertaken specific developmentally important tasks is useful for appraising the interaction of those factors. Depending on the individual case, it may be possible to more clearly state which method of case reasoning is most effective for developing a treatment plan and understanding aspects of prognosis. Ultimately, the clinician is as much interested in the patient's return to prior functional integrity as in symptom remission. Treatment success cannot be proclaimed, for example, in the resolution of psychotic symptoms associated with epilepsy if the patient continues to be socially withdrawn or isolated and no longer capable of independent living.

**Aging** Age and its relation to the expression of illness must be recognized as a changing backdrop for all neuropsychiatric disorders. Age may be used as a convenient indicator for locating the patient in an evolving biological, psychological, and social matrix; a consideration of aging effects cannot await the last stages of the assessment, at which point aging is viewed solely as a factor modifying disease expression. Rather, thoughtful understanding of the aging-related context of a patient's illness is essential to obtaining the fullest view of the relevant life factors contributing to disordered behavior.

**Data Acquisition** The patient's history is an essential feature of neuropsychiatric evaluation because it provides the clinician the opportunity to develop the equivalent of a serial mental status examination across the patient's life course and to identify target symptoms that may respond to treatment. The clinician seeks to discern when, if ever, the patient functioned autonomously and effectively and to define the personal, social, psychological, symptomatic, and medical factors related to primary disease that contributed to a decline in function or to a failure of normal development. The history provides the opportunity to view the unfolding or evolution of signs and symptoms. The clinician strives to develop a variety of corollary information sources when assessing the patient's history so that the most complete view of the illness may be obtained. Corollary information sources may be particularly important for evaluating the history of patients who lack the cognitive capacity to relate their own life stories

effectively and they are especially important for understanding the social and cultural context of specific symptoms.

During the history taking, the clinician seeks to elicit the functional anatomy of an illness. Subtle cognitive disorders, fluctuating symptom pictures, and progressing disease processes may be effectively tracked in 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 fabric of life for each patient provides an invaluable source of data regarding many of the final common behavioral pathways cited previously, including attention and concentration, intellectual abilities, personality, and motor skills, and more typical symptomatic psychiatric features such as mood state and perception. The examiner seeks to find the particular pursuits that the patient has identified as 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 patient-specific settings for monitoring the effects of future therapies.

**Mental Status Examination** Following a thorough history acquisition, the neuropsychiatrist's primary tool is the assessment of mental state. Formal mental status examination fell into disrepute when descriptive psychiatry was seen as irrelevant to the effective implementation of dynamically oriented psychotherapies. Its value is now undisputed. Like the physical examination, the mental status examination is a means of surveying predetermined functions and abilities to allow a definition of personal strengths and weaknesses. It is a repeatable, structured view of symptoms and signs; uniformity of approach assists in the reliable definition of findings and promotes effective communication between 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 to another. Table 10-3 lists the components of a comprehensive neuropsychiatric mental status examination.

**Table 10-3** Neuropsychiatric Mental Status Examination

**General Description** Often, teachers and texts place the so-called sensorium as one of the last items for reporting when describing the mental status examination; the term is too broad, but consideration of arousal and responsiveness to the environment should be one of the first domains of assessment. If the

patient has a significant disorder of attention or arousal, other aspects of the examination may be invalid. Together, attention and comprehension are the pillars of the mental status examination. Problems of arousal and inability to comprehend the fundamental aspects of the examination tend either to invalidate many findings or to warrant caution in their interpretation.

**Language and Speech** The clinician may use language function, particularly when assessing output, to estimate the patient's level of education and intelligence. It is essential, whenever possible, to estimate the patient's premorbid intellectual abilities. Definition of educational attainment during acquisition of the history aids in this process, but further appraisal during mental status assessment is valuable. However, this method must be used carefully because low educational attainment, a different language or cultural background, or acquired brain damage may confound any estimation.

**Thought** Assessment of thought processes involves appraising form and content. Thought form relates closely to language; for example, the clinician must distinguish between fluent aphasia or other disorders of word output and formal thought disorders related to psychosis (such as tangential responses or derailment). There are no ideational or perceptual manifestations that exclusively reflect neuropsychiatric disorders. Although some investigators have emphasized that olfactory hallucinations, for example, indicate brain disease specifically, such assertions have not been supported by well-designed epidemiological studies. Moreover, whereas the major primary psychiatric disorders have no known etiologies, there is no doubt that they involve abnormalities of brain functioning that result in the widest array of symptoms.

**Mood and Affect** When assessing affective and mood state, the examiner should appraise the congruence between expressed mood and demonstrated emotion. Patients with cerebral lesions occasionally demonstrate pseudobulbar affect or affective incontinence. The signs of pseudobulbar affect often include affective overshoot or disconnected affect, in which the patient responds to an appropriate stimulus but the expression is exaggerated or the emotional expression is unrelated to any defined mood. Although such behaviors can be observed in patients with idiopathic or primary psychiatric disorders, careful observation over an extended period often demonstrates that they are distinguishable from behaviors encountered in patients with mood disorders.

**Insight and Judgment** *Insight* denotes looking in while *judgment* reflects looking out. Both entail processes of appraisal or assessment, of one's own state of mind, one's motivations and actions, or one's relationships to others. Discussing the events leading to a clinical evaluation and comparing the patient's version with data gleaned from key informants (family, friends, other clinicians) provide an opportunity to define the congruity of the patient's understanding with that of others. Comparing examination-derived findings with the patient's insight (self-appraisal of mental state) serves as a direct or first-hand assessment.

**Cognition** When testing cognitive functions the clinician should evaluate memory; visuospatial and constructional abilities; and reading, writing, and mathematical abilities. Abstraction ability is also valuable to assess, although a patient's performance on tasks, such as proverb interpretation, may be

difficult to evaluate when abnormal. Proverb interpretation may be a useful bedside projective test in some patients, but 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 a broad array of primary and secondary psychopathological disturbances. Although testing similarities are also education-sensitive, similarities may be more easily understood by patients.

A variety of standardized assessments have been developed in recent decades to assist with mental status evaluation. These include psychopathological rating scales that depend on self-report as well as examiner administration and brief evaluations of cognitive function that have proved helpful in examining individuals with developing cerebral diseases. Clinicians who use brief evaluations, however, must be cautious when interpreting their findings, which are subject to both false-negative and false-positive errors. For example, many tests use single cutoff points as thresholds for establishing abnormality. However, patients with focal lesions who experience discrete intellectual impairments may remain within the normal range of performance. Patients with idiopathic psychiatric disorders, such as major depressive disorder, may perform at abnormal levels on standardized cognitive protocols, inviting unwary clinicians to diagnose them as having dementia. Such assessments may also be susceptible to systematic differences among the elderly and are sensitive to lower educational level. Because they are tools for screening a large number of persons, bedside cognitive tests tend to be least helpful at the extremes, either when appraising highly intelligent individuals who are suffering intellectual declines but remain above the top rung of the test or when testing those who show substantial cognitive decline. The latter may continue to have residual intellectual abilities, some of which may prove helpful for maintenance care, but tests may prove insensitive to assessing those abilities.

## PATHOLOGY AND LABORATORY EXAMINATION

Like 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 there are issues involving etiologically related or comorbid medical conditions. When consulting internists and other medical specialists, the clinician must ask specific questions in order 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. Assignment of a patient's behavioral disturbance to a symptomatic or secondary status reflects, in part, the definition of other nonbehavioral manifestations of the primary disease.

An important element in the description of secondary psychiatric disorders is the use of laboratory assessment procedures to further define the characteristics of the systemic medical or cerebral process that is etiologically related to the psychiatric symptoms in question. This requires that psychiatrists understand the range of disorders that can lead to behavioral abnormalities. A screening laboratory evaluation is sought initially and may be followed by a variety of ancillary tests to increase the diagnostic specificity. Table 10-4 lists such procedures.

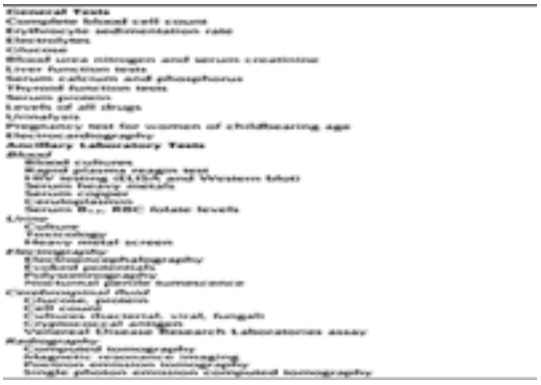

**Table 10-4** Screening Laboratory Tests

A clinician requesting specific laboratory tests should be led by informed clinical suspicion as well as by an appreciation of the relative costs and benefits of each test. With the exception of low-cost screening procedures, few tests should be requested without a clearly defined rationale. Different approaches are taken for inpatients versus outpatients and for those with regular medical care versus those who have none. Repetition of recently performed tests is often without value.

## Electroencephalography

EEG is an easily accessible, noninvasive test of brain dysfunction that has a high sensitivity in 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 where the patient remains conscious although behaviorally impaired. EEG is also sensitive to metabolic and toxic states, often showing a diffuse slowing of brain activity. Focal slowing, when present, may be indicative of a variety of causes such as space-occupying lesions (tumors, cerebral abscesses) or subdural hematomas. However, a superficial EEG (one that is recorded through the skull) is often insufficient for source localization and may prove insensitive to a variety of abnormal processes, necessitating nasopharyngeal recording to better define abnormalities generated by the temporal lobes or direct cortical (surface) recording to localize seizure foci. The EEG findings change with aging, with a general reduction in alpha wave activity, and with increases in the relative amounts of theta and delta wave activity. Early in the course of disorders such as Alzheimer's disease the standard EEG finding usually remains normal and therefore is often unrevealing. As part of sleep polysomnography, recent studies have suggested that the EEG may aid in the future in the distinction between elderly subjects with major depressive disorder associated with cognitive impairment and those with a primary neurodegenerative process underlying their dementia.

## Computed Tomography and Magnetic Resonance Imaging

CT scanning and 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, designated by such terms as *rims, caps, unidentified bright objects*, and *leukoaraiosis*, remains to be defined. Such abnormalities are detected in younger patients with multiple sclerosis or HIV infection and in older patients with hypertension, vascular dementia, or dementia of the Alzheimer's type. However, their prevalence is also increased in healthy, aging individuals who have no defined disease processes. At present, those types of findings should be viewed in the same light as one would consider atrophic changes; namely, they are detected in a highly sensitive fashion but are usually nonspecific or nondiagnostic in meaning. White matter hyperintensities are more extensive and more frequent in individuals with disease, particularly those with disorders involving cognitive dysfunction, but they are too variable to contribute to the diagnosis or prognosis in an individual case. Like CT, the greatest utility of MRI when used in the evaluation of patients with dementia arises from what it may exclude (tumors, vascular disease) rather than what it can demonstrate specifically.

Because of MRI's ability to delineate brain anatomy and its sensitivity to white matter changes, these guidelines remain utilitarian when modified appropriately. Indications for ordering MRI in psychiatric patients include (1) delirium or dementia of unknown etiology; (2) a first episode of psychosis of unknown etiology; (3) a movement disorder of unknown etiology; (4) the initial evaluation of anorexia nervosa; (5) prolonged catatonia; (6) the initial onset of a major mood disorder or personality change after age 50 years; (7) the presence of unanticipated behavioral, intellectual, or functional decline in an already diagnosed psychiatric patient in whom the clinician would normally expect long-term stability or, at worst, a relapsing-remitting course with a return to baseline between episodes; and (8) the presence of any new behavioral or intellectual disorder in a patient infected with HIV.

Imaging studies have been overused in the periodic monitoring or reassessment of patients with suspected dementia of the Alzheimer's type in whom earlier examinations showed characteristic cerebral changes. Unless one suspects a missed diagnosis of normal pressure hydrocephalus, or perhaps failure to detect microinfarctions on CT when such a finding on MRI might have ruled out Alzheimer's type, repeated scans are not warranted.

Occasional patients may become agitated in the MRI tube; premedication with a benzodiazepine can minimize the problem. The magnetic field prohibits use of MRI in patients with pacemakers or metal implants, including metallic surgical clips, although many patients now receive MRI-compatible clips at surgery.

### Positron Emission Tomography, Single Photon Emission Computed Tomography, and Functional Magnetic Resonance Imaging

Physiologically based techniques for imaging the brain, such as PET and SPECT, involve the injection of radioactively labeled, naturally occurring compounds or a radiopharmaceutical, with subsequent demonstration of cerebral blood flow or the incorporation of the labeled compounds into specific

metabolic pathways. Such imaging methods have shown promise in studying the neurochemical and physiological bases of a variety of neuropsychiatric disorders. However, the cost of PET currently precludes its use as a routine diagnostic procedure, and there are insufficient data to project its ultimate utility for routine clinical evaluation. SPECT can be performed more readily and more cheaply, but whether it will have specific diagnostic utility in general psychiatry remains to be determined. Functional MRI (fMRI) holds great promise as a research tool to explore the physiological bases of complex behavioral processes. However, its potential utility as a clinical diagnostic tool remains to be defined.

### 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. For example, many tests do not have appropriate aging-related norms (because they have been used primarily in young and middle-aged adults who are better educated) and therefore are less useful when used in children or the elderly. In general, clinicians should understand that a variety of distinct, competing neuropsychological schools of thought have developed different views regarding methods of individual evaluation, use of the tests, and interpretation of the data. Because neuropsychological evaluation is evolving rapidly and provides a remarkable array of tools for assaying disordered behavior, sophistication in the use and interpretation of those tests will benefit the clinician.

## ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

**Factors Affecting Disease Presentation** Neuropsychiatric evaluation and diagnosis are based on a fundamental understanding of the mechanisms by which pathobiological processes, both systemic and cerebral, express themselves through altered CNS function. The factors that influence symptom expression can be approached from several perspectives.

The first perspective relates to what might be called mode of action. Systemic disorders typically express themselves indirectly, through as yet undefined centrally active substances, defined endocrine disruptions, or fundamental metabolic alterations. Their effects tend to be generalized but often include delirium, dementia, or mood disturbance. In contrast, selective destruction of specific brain regions is more frequently associated with decrements in discrete cognitive tasks or behaviors. One must be cautious with such generalizations, however, as focal lesions in key brain regions (such as those involving brainstem structures) may cause delirious states. Moreover, the clinician may encounter substantial variability in the range of behavioral abnormalities caused by specific focal damage.

A second perspective relies on knowing the natural history of particular pathological processes. Diseases

tend to progress or unfold in characteristic fashions, thus allowing for continuing differential diagnostic consideration over time. Also, meaningful prognosis depends on a thorough appreciation of natural history.

A third perspective derives from recognizing the timing of an insult within a neurodevelopmental framework, where the long-term impact of any process or event will depend in part on the compensatory or recovery capacities of the brain. Such capacities change as part of the aging process (they may be fundamental to aging), but much remains unknown.

A final perspective has to do with the types of cells and regions damaged by specific diseases. Degenerative disorders (Huntington's disease, Parkinson's disease) often lead to destruction of neurochemical systems. Hypoperfusion or pulmonary insufficiency both cause hypoxia, which in turn affects regions with especially vulnerable cell populations (such as the hippocampus) or regions near the ends of vascular trees (the so-called watershed zones, including many brain association areas). Lesions due to ischemic and hemorrhagic cerebrovascular disease reflect vascular anatomy rather than the pathoanatomy associated with degeneration of functionally significant neurochemical systems. Brain toxins may act by binding to specific neurochemical receptors, causing differential damage in direct proportion to regional variations in receptor concentration. Knowledge of the cell populations and anatomical regions affected, when integrated with the other perspectives, assists in understanding or anticipating the full effects of the primary disorder.

A variety of disorders can lead to behavioral abnormalities. They can be subsumed under the following broad categories: trauma, tumor, infection, immune and autoimmune disorders, cardiovascular disease, congenital and hereditary conditions, physiological disorders, primary psychiatric disorders, metabolic disorders, demyelinating disorders, degenerative diseases, substance-induced disorders and disorders due to toxins, and malingering.

**Trauma** Head trauma leading to brain injury is a possible cause for delirium, dementia, and amnestic disorder, as well as all of the secondary psychiatric syndromes. Traumatic brain injury is largely a disease of modernity, with the majority of injuries resulting from motor vehicle accidents, gunshot wounds, or occupational mishaps. Estimates point to an annual incidence of 400 to 600 cases per 100,000 population, but such figures must be viewed with caution in light of variable definitions at the less severe (mild) end of the injury spectrum.

**Pathophysiology** Head trauma can cause brain injury through multiple mechanisms, both direct and indirect. Table 10-5 lists the factors that contribute to brain injury after head trauma. The clinician must recognize that brain injury from head trauma often results in pathology in areas beyond the site of direct impact. In addition, certain areas of the brain are more susceptible to injury regardless of the site of impact (Fig. 10-1). Those areas include the orbitofrontal and frontal pole convexities as well as the anterior temporal lobes, which lie close to bony skull prominences. Rotational and horizontal movements can produce shearing in areas of the brain that are relatively immobile, such as central white matter fiber pathways. Shearing forces can produce diffuse and extensive damage, also unrelated to the

actual site of impact. Thus, frontal, subcortical, and limbic structures are especially vulnerable to traumatic head injury. This may explain the diversity of neuropsychiatric sequelae and the occasional occurrence of disproportionate disruptions in personality, behavior, and affect when cognitive and motor functions are largely spared. Penetrating head injuries or injuries in which the head has not been able to rotate or move may spare patients from the extensive injuries associated with indirect effects, despite significant direct damage. Bullet or penetrating missile injuries, however, may disrupt neuronal function beyond the site of impact through the effects of high-frequency vibratory waves.

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|---|
| **Direct Effects** |
| Contusion underlying point of trauma (coup) |
| Contusion linearly opposite point of trauma (contrecoup) |
| Compression from overlying depressed skull fracture |
| Compression from overlying hematoma |
| **Indirect Effects** |
| Diffuse impact damage |
| Widespread damage in cerebral white matter |
| Discrete lesions in corpus callosum |
| Discrete lesions in rostral brainstem |
| Common cortical contusions independent of direction of impact |
| Orbitofrontal |
| Anterior temporal |
| Frontopolar |
| Secondary cerebral processes |
| Cerebral edema |
| Increased intracranial pressure with central herniation (Duret's hemorrhages) |
| Increased intracranial pressure with uncal herniation and posterior cerebral artery entrapment (medial occipital infarction) |
| Multifocal ischemic changes |
| Contributing secondary systemic processes |
| Shock (blood loss, ruptured viscera, sepsis, etc.) with hypotension |
| Pulmonary failure with anoxia |
| Long bone fracture with fat emboli |

*Adapted from Alexander MP: Traumatic brain injury. In Psychiatric Aspects of Neurologic Disease, vol 2, DF Benson, D Blumer, editors. Grune & Stratton, New York, 1982.*

**Table 10-5** Pathophysiological Mechanisms of Brain Injury After Head Trauma

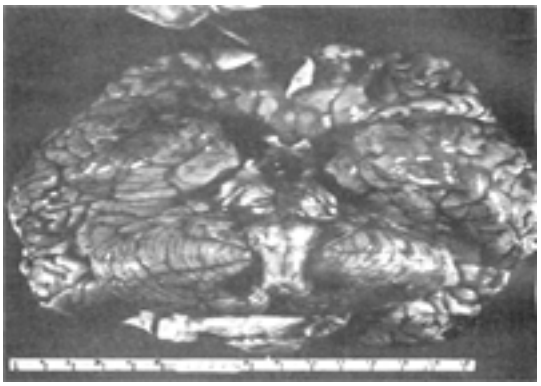
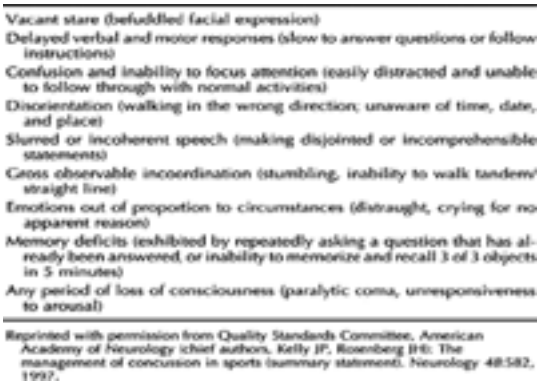


**FIGURE 10-1** Severe contusion of the frontal poles has resulted in their atrophy and distortion. (Courtesy of H. M. Zimmerman, M.D.)

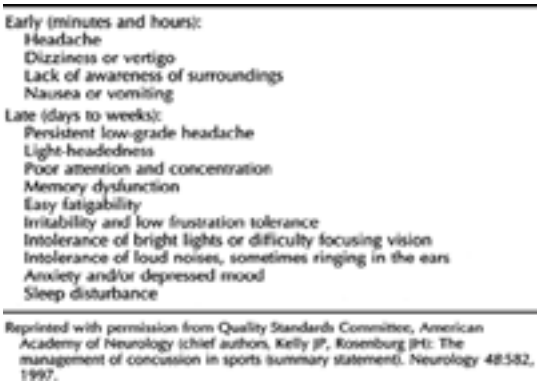
**Psychiatric Symptoms** Delirium is the acute manifestation of all head injuries that are likely to produce long-lasting sequelae. In severe head injury there is an initial loss of consciousness (coma), followed by gradual recovery, with the delirium taking the form of progressive stages of semiwakefulness, distractibility, and confusion, and finally a stable level of consciousness. The entire process may be brief or may take hours to weeks. In milder injuries there may be a brief absence of consciousness, such as momentary dazing, passing out, or transient confusion. A brief lapse or alteration of consciousness occurring after head trauma is defined as *concussion*. Table 10-6 includes frequently observed features of concussion and Table 10-7 lists common symptoms. Table 10-8 divides concussion cases into three grades of severity. Grades 2 and 3 cases require neurological evaluation; Grade 3 cases warrant immediate transport to an emergency department for assessment.



Vacant stare (befuddled facial expression)
Delayed verbal and motor responses (slow to answer questions or follow instructions)
Confusion and inability to focus attention (easily distracted and unable to follow through with normal activities)
Disorientation (walking in the wrong direction; unaware of time, date, and place)
Slurred or incoherent speech (making disjointed or incomprehensible statements)
Gross observable incoordination (stumbling, inability to walk tandem/straight line)
Emotions out of proportion to circumstances (distraught, crying for no apparent reason)
Memory deficits (exhibited by repeatedly asking a question that has already been answered, or inability to memorize and recall 3 of 3 objects in 5 minutes)
Any period of loss of consciousness (paralytic coma, unresponsiveness to arousal)

Reprinted with permission from Quality Standards Committee, American Academy of Neurology (chief authors, Kelly JP, Rosenberg JH): The management of concussion in sports (summary statement). Neurology 48:582, 1997.

**Table 10-6** Frequently Observed Features of Concussion



Early (minutes and hours):
Headache
Dizziness or vertigo
Lack of awareness of surroundings
Nausea or vomiting
Late (days to weeks):
Persistent low-grade headache
Light-headedness
Poor attention and concentration
Memory dysfunction
Easy fatigability
Irritability and low frustration tolerance
Intolerance of bright lights or difficulty focusing vision
Intolerance of loud noises, sometimes ringing in the ears
Anxiety and/or depressed mood
Sleep disturbance

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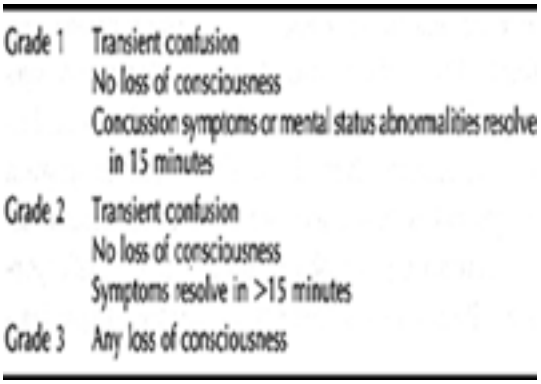
**Table 10-7** Symptoms of Concussion



| | |
|---|---|
| Grade 1 | Transient confusion<br>No loss of consciousness<br>Concussion symptoms or mental status abnormalities resolve in 15 minutes |
| Grade 2 | Transient confusion<br>No loss of consciousness<br>Symptoms resolve in >15 minutes |
| Grade 3 | Any loss of consciousness |

**Table 10-8** Gradations of Concussion

Cognitive disorders are frequent after traumatic brain injuries. Global impairment may be seen after extensive head injury or prolonged coma, although those deficits may improve dramatically in the months following injury. Dementia or a persistence of global cognitive impairment is less common, reflecting the high mortality associated with more severe injuries. When dementia is seen, it is usually associated with hemiparesis, aphasia, or other indicators of severe and extensive injury.

Persisting dementia with gradually progressive deficits may be associated with multiple recurrent head traumas. The condition has been termed chronic traumatic encephalopathy and has been noted to occur after even minor multiple head traumas. Dementia pugilistica, or boxer's dementia, is an example. Onset usually occurs at the end of a boxer's career but chronologically earlier than the onset of the degenerative dementias. A subcortical pattern of dementia (discussed later under degenerative diseases) is typically present, with prominent parkinsonian features as well as dense memory impairment. Neuropathological

studies have demonstrated global atrophy with specific involvement of the midbrain and mesial temporal lobe, presumably reflecting the direct and indirect effects of multiple injuries. Plaques and tangles are often noted, but the pathophysiological mechanism remains unknown.

Memory disturbance is nearly always present with any trauma severe enough to cause a concussion. *Posttraumatic amnesia* occurs invariably after concussive brain injury and refers to the inability to register new memory. The duration of posttraumatic amnesia, which may be very brief, is a significant indicator of severity but can be assessed only after the patient has regained a stable level of consciousness. *Retrograde amnesia* is the inability to recall events prior to the injury. It can be assessed by asking patients about their last memories before the injury. Retrograde amnesia generally shrinks with recovery whereas a postinjury memory deficit tends to remain constant; patients do not recover memories from the period of posttraumatic amnesia. Additionally, patients may suffer persisting impairment of new learning and recall (an amnestic disorder) as a result of permanent pathological changes incurred because of the traumatic event. Persisting specific deficits in the context of overall robust recovery can be disabling and frustrating for the patient, who appears normal to others although still impaired cognitively and functionally. Depending on the specific nature of any deficits, these patients would be diagnosed according to DSM-IV as having cognitive disorder not otherwise specified or amnestic disorder due to traumatic brain injury.

*Postconcussional disorder* is a disabling cluster of symptoms of uncertain pathophysiology. It emerges within hours to days (or a few weeks) of a mild head injury and is characterized by headache, dizziness, fatigue, poor concentration and mild memory impairment, problems sleeping, irritability, anxiety, and often significant problems with mood regulation or frank clinical depression. Diminished spontaneity, apparent apathy, and other personality changes are noted also. The cluster of symptoms is remarkably consistent from patient to patient. Table 10-9 presents the proposed research diagnostic criteria for postconcussional disorder that are included in DSM-IV.

**Table 10-9** DSM-IV Research Criteria for Postconcussional Disorder

ICD-10 defines postconcussional syndrome as follows:

> The syndrome occurs following head trauma (usually sufficiently severe to result in loss of consciousness) and includes a number of disparate symptoms such as headache, dizziness (usually lacking the features of true vertigo), fatigue, irritability, difficulty in

concentrating and performing mental tasks, impairment of memory, insomnia, and reduced tolerance to stress, emotional excitement, or alcohol. These symptoms may be accompanied by feelings of depression or anxiety, resulting from some loss of self-esteem and fear of permanent brain damage. Such feelings enhance the original symptoms and a vicious circle results. Some patients become hypochondriacal, embark on a search for diagnosis and cure, and may adopt a permanent sick role. The etiology of these symptoms is not always clear, and both organic and psychological factors have been proposed to account for them. The nosological status of this condition is thus somewhat uncertain. There is little doubt, however, that this syndrome is common and distressing to the patient.

At least three features of the syndrome are necessary for diagnosis, according to ICD-10 (Table 10-10). Laboratory tests may be helpful for corroboration. Some observers have argued that the requirement in DSM-IV to wait 3 months before a definitive postconcussional diagnosis may lead to a delay in establishing a proper diagnosis and initiating therapy for some patients. Indeed, postconcussional conditions transiently or spontaneously resolve for most affected individuals, with symptom remission during the first 3 to 6 months following injury. Although occasional individuals develop posttraumatic migraine, patients with postconcussional disorder more commonly describe symptoms reminiscent of muscle tension headaches arising frontally or posteriorally and occasionally involving temporal regions as well. Some report tenderness persisting at the site of impact, but that is less frequent and its pathophysiological basis is unknown. Major depression in the context of postconcussional disorder may not remit unless specific antidepressant treatment is initiated. Postconcussional symptoms that persist beyond 12 weeks should raise suspicions of additional brain pathology, such as an undetected subdural hematoma or a chronic cognitive impairment syndrome. A thorough evaluation is warranted. Postconcussional headaches can persist and prove disabling, and patients may benefit from the judicious use of analgesic as well as antidepressant agents. However, clinicians also must be vigilant regarding the development of headaches caused by analgesic rebound, a paradoxical but common cause of apparent chronic posttraumatic headaches. Secondary mood disorders are commonly seen with severe injury, although they may be more common after minor injury as part of the postconcussional syndrome. All forms of psychotic symptoms that are seen in idiopathic schizophrenia can be seen after traumatic injury. They are most common in the immediate delirious period but can persist once a stable level of consciousness has been obtained.

**Table 10-10** ICD-10 Diagnostic Criteria for Personality and Behavioral Disorders Due to Brain Disease, Damage and Dysfunction

**Personality Change Due to a General Medical Condition** This disorder is a frequent concomitant of traumatic brain injury, owing to the vulnerability of the frontal lobes and the important role those structures play in the expression of personality. Two personality syndromes have been described with frontal lobe injury: the *orbitofrontal syndrome*, characterized by disinhibition, explosiveness, and jocularity; and the *frontopolar syndrome*, characterized by apathy, behavioral inertia, and indifference. Patients may appear indifferent to their incapacities or may confabulate regarding their injury and hospitalization. Less marked personality changes, such as irritability and a so-called short fuse, are common, especially as part of the postconcussional syndrome.

Adjustment disorders can occur at any point once a stable level of consciousness has been attained. Patient and family must adjust to loss of capacity, increased irritability and fatigue, a possible change in family roles, absence from work, financial constraints, and legal entanglements. As in all adverse circumstances, premorbid personality heavily influences the patient's adaptive capacities. Unfortunately, clinicians have at times seen the presence of an adjustment disorder or a prior history of maladaptive personality functioning as a reason to conclude that patients are not suffering from behavioral or cognitive impairments arising from brain injury. The evaluation and treatment of head trauma require clinical flexibility to address the broadest range of symptoms and syndromes.

**Course and Prognosis** The course of recovery from posttraumatic syndromes depends on the severity of the initial injury and the location of damage. The duration of coma and of posttraumatic amnesia may be useful prognostic indicators. Dramatic improvements can occur within days and continue for up to 6 months. Overall recovery may continue up to 24 months, with motor and physical improvement often preceding behavioral and cognitive restoration; less frequently, recovery continues beyond 2 years after injury. The neurobiological mechanisms leading to recovery are unknown.

**Treatment** There are no specific treatments for the cognitive abnormalities associated with head trauma. Life-sustaining and life-supportive short-term therapies may be needed initially, and the psychopathological conditions resulting from head trauma may warrant symptomatic therapies. Despite a boom in institutions and companies offering cognitive rehabilitation, it remains unproved scientifically whether those methods significantly augment natural recovery processes.

**Litigation** The high frequency of closed head injuries and posttraumatic complaints, together with the ready availability of psychiatrists, neurologists, and psychologists willing to testify as “experts,” have combined with lawyers in today's litigation-prone culture to bring postconcussional disorder center stage in American courtrooms. While there are numerous instances of claims related to bona fide cognitive, emotional, and behavioral deficits resulting from brain injury, it also is clear that many are unsubstantiated. There appear to be four often interacting factors that contribute to the latter situation: (1) Absence of concussion—Suits frequently request damages for postconcussion syndrome (or a related term) when a careful review of medical records reveals no evidence of pertinent symptoms or signs, such as altered consciousness, posttraumatic amnesia, nausea and vomiting, photophobia, or headache: (2) Nonspecific symptoms—Postconcussional disorder is diagnosed due to fatigue, headache, and dysphoria in the absence of symptoms or signs of concussion; complaints may have developed weeks or even months after an accident or injury. (3) Diagnostic mythology—Once a clinician labels a condition

postconcussional without substantiation, this label is then promulgated and other clinicians accept it at face value without an independent review of all necessary data. The diagnosis soon assumes mythic proportions. (4) Lack of common sense—[A patient is diagnosed as having specific posttraumatic psychopathology or cognitive decline without the earlier medical, psychiatric, educational, and vocational records having been reviewed, which reveals the presence of the claimed symptoms or signs before the purported brain injury.]

In all litigation-related evaluations, the possibility of malingering needs to be considered. Relevant hints or clues include: a substantial discrepancy between mild clinical findings and severe or dramatic subjective complaints; relatively intact personal and vocational functioning and markedly abnormal neuropsychological test scores; vague complaints without objective test or functional correlates; disparity between complaints of vocational limitations and continued vigorous recreational activities (e. g., hunting, weight training, volleyball, or tennis); a history of legal difficulties or multiple accident claims; evidence of a clinically significant personality disorder.

An evaluator must also be vigilant to assess whether there is evidence of an undiagnosed mood disorder. Frequently an individual with severe physical injuries gradually develops complaints of dysphoria, headaches, poor concentration, and memory dysfunction. Diagnosed as suffering a postconcussional disorder, the plaintiff or patient believes he has permanent brain damage rather than an eminently treatable mood disorder.

**Tumor** Intracranial tumors, whether of primary CNS or metastatic origin, can cause behavioral disturbances by directly affecting brain function. They may do so by destroying or compressing brain parenchyma (from mass effect or edema), through obstructive hydrocephalus, or by disrupting brain vasculature (Fig. 10-2). The nature of the ensuing behavioral disturbance depends on factors already discussed, such as time course and injury location.

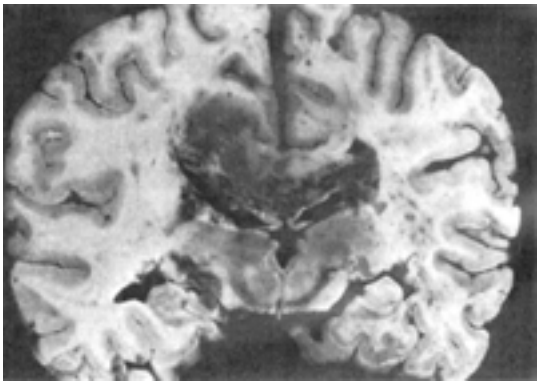


**FIGURE 10-2** Glioblastoma multiforme. The massive tumor crosses the midline in the corpus callosum. (Reprinted with permission from Hirano A: *A Guide Neuropathology*. Igaku-Shoin, New York, 1981.)

Extracranial nonbrain neoplasms may indirectly alter brain function and cause psychiatric symptoms by any of several pathways. The cancer may disturb one or more organ systems known to affect brain function. For example, lung cancer may cause hypoxemia and metastatic prostate carcinoma may lead to obstructive uropathy with consequent renal failure. Paraneoplastic syndromes may lead to metabolic

abnormalities (e.g., hypercalcemia) commonly associated with behavioral changes. Intriguingly, cancer may cause psychiatric symptoms without any known metabolic or other organ system disturbance; a commonly cited example is the onset of a major depressive disorder as the first clinical manifestation of occult pancreatic carcinoma. The mechanisms of such phenomena are unknown, although it has been speculated that blood-borne humoral factors secreted by the tumor are centrally active.

**Infection** Infections can produce any of the range of cognitive impairments or secondary syndromes that are sudden or insidious in onset. Acute infectious processes involving the CNS often produce delirium as a component of fulminant deterioration. Chronic psychopathology can result either from a chronic infectious process, such as neurosyphilis or Creutzfeldt-Jakob disease, or from persisting structural brain damage incurred as a result of an acute infection, as in the long-term sequelae of herpes simplex encephalitis.

**Syphilis** Syphilis is a chronic infection resulting from inoculation with the spirochete *Treponema pallidum*. It is transmitted through sexual contact. Primary syphilis is a local disease manifested by a lesion at the site of inoculation, usually the penis, vagina, or mouth, within 2 to 3 weeks after inoculation. Secondary syphilis, manifested by a recurrent rash occurring anywhere on the body but especially on the palms and soles, has its onset 6 weeks to 6 months after initial exposure. After the rash resolves, syphilis may enter a latent stage that lasts 2 to 10 years after inoculation; serology remains positive throughout the latent stage. Tertiary syphilis may involve skin, bone, and the aorta, as well as the CNS. Neurosyphilis can occur 5 to 35 years after the initial inoculation. Neurosyphilis is divided into four stages: (1) an asymptomatic stage, without symptoms but with abnormal cerebrospinal fluid (CSF); (2) meningovascular syphilis, characterized by headache, nuchal rigidity, irritability, and delirium; (3) tabes dorsalis, with signs of posterior column degeneration, such as ataxia (due to loss of proprioception resulting in a slapping or high-stepping gait and trophic joint changes—Charcot's joints), areflexia, paraesthesias (described as lightning pains and typically involving the extremities), incontinence, impotence, and abnormal pupillary findings (the classic Argyll Robertson pupil, which accommodates but does not respond to direct light response); and (4) general paresis, also known as general paralysis of the insane, dementia paralytica, or paretic neurosyphilis, the classic neuropsychiatric disorder of tertiary syphilis (Fig. 10-3).

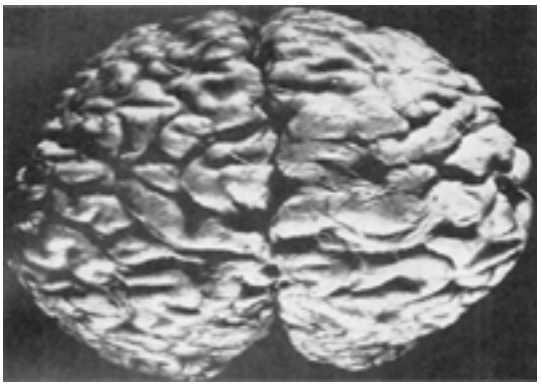


**FIGURE 10-3** Paretic neurosyphilis. Thickening of the meninges and atrophy of the cerebral convolutions. (Reprinted with permission from Merritt HH, Adams RD, Solomon HC: *Neurosyphilis*. Oxford University Press, New York, 1946.)

General paresis has great significance for the history of psychiatry because it was one of the first

instances in which severe behavioral and cognitive disturbances could be attributed directly to an etiologically definable brain disease. General paresis can present as almost any form of psychiatric disturbance or dementia syndrome. The classically described grandiose presentation has become rare whereas depressive presentations have become more common. Often a general change in personality is the initial presentation, with apathy, lability, and coarsening of behavior. Dementia is of a mixed pattern, with prominent impairment of memory, language, and judgment, as well as loss of initiative and psychomotor slowing. Neuropathologically the brain demonstrates diffuse degeneration with marked lymphocytic infiltration throughout.

**Creutzfeldt-Jakob Disease** *Creutzfeldt-Jakob disease* is an infection that causes a rapidly progressive cortical-pattern dementia. The infectious agent, a *prion*, is a subviral replicative protein that is now known to cause a variety of so-called spongiform diseases in animals and humans. The 1998 Nobel Prize for Medicine was awarded to Stanley Prusiner for his work describing this novel biological entity. The age at onset of Creutzfeldt-Jakob disease is usually in the sixth or seventh decade, although onset can occur at any age. The incidence is 1 in 1,000,000. The clinical symptoms vary with progression of the illness and depend on the regions of the brain that become involved. Patients may present initially with nonspecific symptoms, including lethargy, depression, and fatigue. Within weeks, however, more fulminant symptoms develop, including progressive cortical pattern dementia, myoclonus, and pyramidal and extrapyramidal signs. Although blood, CSF, and imaging studies are unremarkable, the EEG can demonstrate a characteristic pattern of diffuse symmetric rhythmic slow waves. A presentation with rapid deterioration, myoclonus, and the characteristic EEG pattern should raise suspicion of Creutzfeldt-Jakob disease. The definitive diagnosis is made by postmortem microscopic examination, which demonstrates spongiform neural degeneration and gliosis throughout the cortical and subcortical gray matter; white matter tracts are usually spared. Prion disease can incubate for decades before the emergence of clinical symptoms and subsequent rapid progression. Reported routes of transmission include invasive body contacts, such as direct tissue transplantation (e.g., corneal transplants) or hormonal extracts (e.g., human growth hormone, before synthetic supplies were developed). Familial patterns have also been reported, which suggests that there may be genetic susceptibility to infection or vertical transmission of the disease agent. No antiviral agents have been shown to be effective in retarding or slowing disease progress, although amantadine (Symmetrel) has been reported occasionally to have had some success. Death usually ensues within 6 months to 2 years of onset. During the past several years, a pathologically similar condition, bovine spongiform encephalopathy, has been described. Diagnosed primarily in the United Kingdom, this disease underscores the effects of modern animal husbandry methods on the amplification of rare diseases and the continuing threat of zenobiotic transmission of these to humans.

**Viral Encephalitis** Viral encephalitis varies in severity, depending on the specific etiological agents. Mild disease is more common with mumps, and enteroviral infections can be limited to headache and malaise. Severe disease is characteristic of infections such as rabies and herpes simplex. Herpes simplex encephalitis is the most common of the severe nonepidemic encephalitides. It is of interest to neuropsychiatry because of the preferential involvement of the orbitofrontal and medial-temporal regions of the brain. A typical presentation consists of severe encephalitis of rapid onset, high fever, headache, nuchal rigidity, focal neurological signs, and delirium. Rarely, a sudden, transient psychosis

may herald the onset. Occasionally the onset is more insidious, with the clinical picture at presentation limited to personality change or memory impairment. Necrosis of the frontal and temporal lobes can occur rapidly. Mortality is high: approximately 70 percent. Whenever herpetic encephalitis is suspected, a definitive diagnosis should be made as rapidly as possible by brain biopsy, with the subsequent urgent initiation of antiviral therapy. Survivors may sustain deficits related to temporal and frontal lobe damage, including a dense amnesia disproportionate to the degree of other intellectual impairment; hallucinations in all spheres, including olfactory and gustatory; components of a Kluver-Bucy syndrome; partial complex seizures; aphasia; and anosmia.

**Human Immunodeficiency Virus** HIV-1 has created a late–twentieth-century epidemic parallel in severity and pervasiveness to the scourges of bygone eras. Acquired immune deficiency syndrome (AIDS), the later stages of HIV infection, has been recognized since the 1980s. In recent years its neuropsychiatric manifestations have become a focal point for diagnosis and therapy, as patients live longer through the use of partially effective antiviral therapies and a variety of second-line medications employed for treating opportunistic infections. The following discussion focuses on neuropsychiatric phenomena that appear to result from HIV-1 action in the brain.

Mr. Zeigler is a 55-year-old, married, Latin American businessman who is hospitalized with an 8-month history of diarrhea, fatigue, and weight loss. He has sought help from several institutions both in the United States and Europe, but his illness remains undiagnosed. A psychiatric consultation is requested because both the patient and his physician think he is depressed and wonder what role this might play in his weight loss and overall condition.

Mr. Zeigler gives a detailed history of his family's emigration from Europe when he was a child, his personal success in business, and the progressive difficulty he has been experiencing because of his weight loss and fatigue. He has lost 85 pounds over the 8 months and now has to force himself to eat. In the past, eating had been a great pleasure for him and he considered himself a gourmet cook. Although he complains of some difficulty with his memory and concentration, he continues to manage a multinational business and to conduct complex financial deals. He says he feels sad but is hopeful that the diagnosis can be made quickly. He conducts himself in the same autocratic manner in the hospital that he is accustomed to displaying in business and with his family. He has many interests, including an active sex life, which he wishes to resume once he regains his strength.

Mrs. Zeigler confirms her husband's history and speaks of his complete control of his business and of the family's financial affairs. She describes how this has created conflicts with her sons, who resent their father's unyielding control, even though they work in the family company. It is her opinion that her husband is depressed and that this is the cause of most of his symptoms. In response to questions about his activities, she agrees that his fatigue seems the only obstacle to pursuing his interests. She cannot answer any questions about his sex drive because she stopped having sex with him 10 years before this illness. He accepted this, and she presumed he frequented prostitutes.

Over the next few days Mr. Zeigler's condition deteriorates markedly, and he is thought to have had a stroke because of some slurred speech and a slight weakness of the right side of his body. He then becomes short of breath and is admitted to the intensive care unit. A chest X-ray suggests *Pneumocystis carinii* pneumonia, which is confirmed by bronchoscopy. He does not respond to co-trimoxazole (Bactrim) and is started on pentamidine (NebuPent). While in the intensive care unit Mr. Zeigler is delirious, frequently hallucinating, and often incoherent in both Spanish and English. His children fly to the United States because he is not expected to survive. This prediction proves to be incorrect, and his pneumonia resolves after several weeks of treatment. A CT scan of the brain suggests a CNS infection with toxoplasmosis, and examination of the stomach by endoscopy leads to the diagnosis of gastrointestinal *Isospora*. Surprisingly, all these infections respond to treatment.

It is now clear that Mr. Zeigler has AIDS, and his physician presents this diagnosis to him along with an inquiry about his sexual experiences. Mr. Zeigler is enraged by his doctor's implication of homosexuality and adamantly denies any homosexual activity. He discusses his adaptation to his wife's decision to cease sexual activity with him. He has frequented prostitutes in the Far East, where he traveled regularly on business. It seems impossible to him that he might have AIDS, although he admits to having contracted syphilis 4 years before his current illness. On discharge, Mr. Zeigler is given the diagnosis of AIDS, with the only clear risk factor his sexual contact with prostitutes.

Six months later Mr. Zeigler and his wife return to the United States for further evaluation of his mental status. His wife is concerned that he has become depressed because he is no longer able to handle his financial affairs. She feels his personality has undergone a radical change in that he no longer seems to care about anything, in spite of the fact that his appetite has returned to normal and he has regained much of his lost weight. Much of his time is now spent sitting idly in their garden.

When examined, Mr. Zeigler appears to be in good physical health. However, his mental condition has obviously deteriorated; it is not possible to conduct an interview in English although previously he had spoken several languages fluently. He smiles pleasantly, but is both disoriented and confused, even when speaking in Spanish. This surprises even his wife, since she had not been aware of this change in his cognitive functioning. He has poor short-term memory and cannot perform simple calculations. His remote memory is intact, although his wife feels that he has confused some historical events. Mr. Zeigler seems unaware that there are any deficits in his intellectual functioning. Medical evaluation does not reveal any active infections. (Reprinted with permission from *DSM-IV Casebook*.)

Clinicians began to recognize the variety of neuropsychiatric manifestations of HIV in the mid-1980s. Most prominent were major mood disturbances (major depressive, dysthymic, and less commonly, bipolar disorders) and a characteristic progressive cognitive impairment that was labeled AIDS dementia complex. Rarely, patients developed psychoses, at times with a schizophrenic presentation, as well as

alterations of personality. Later, carefully conducted epidemiological studies revealed that persons at highest risk for HIV infection suffered elevated rates of mood and substance use disorders before contracting the disease. Intertwined with syndromes that were thought to be direct results of primary HIV infection of the CNS or secondary complications from other infections or tumors were a variety of adjustment and mood disturbances, reflecting responses to a progressive, inevitably terminal disease.

The psychopathological manifestations of HIV cover the major symptom clusters, as well as AIDS dementia complex and delirium. Clinicians have used empirical treatments, many with substantial symptomatic response. Intervention with antiviral therapies also has shown beneficial behavioral effects, especially when CSF indices of CNS infective activity have suggested that the primary disease has increased in its activity. However, there have been few carefully conducted therapeutic trials to establish the overall efficacy of any symptomatic psychopharmacotherapy.

AIDS dementia complex is characterized predominantly by a subcortical presentation, with prominent psychomotor slowing and difficulties with concentration and memory. Early associated motor deficits include ataxia, leg weakness, tremor, and loss of fine motor coordination. Patients commonly become apathetic or withdrawn. The course is steadily progressive, at times punctuated by abrupt acceleration. Like other dementing disorders, AIDS dementia complex progresses to a late stage characterized by severe dementia, mutism, incontinence, paraplegia, and in some cases, myoclonus.

During the latter part of the 1980s, controversy developed regarding the temporal sequence of the emergence of cognitive abnormalities versus other symptoms reflecting the advance of HIV infection to full-blown AIDS. There is no dispute that AIDS dementia complex may be the predominant feature of AIDS for some patients, but there is uncertainty regarding the presence of cognitive abnormalities in patients who are both clinically asymptomatic and without laboratory evidence of encroaching immune suppression. Many patients with HIV develop a mild (minor) cognitive disorder that has many of the same features of AIDS dementia complex but that is as not cognitively severe or as impairing functionally. Recently, an American Academy of Neurology AIDS Task Force developed a set of standard nomenclature for neurological manifestations of HIV-1 infection, including both cognitive and peripheral neurological findings.

In autopsy series, 75 to 90 percent of brains of patients dying from HIV infection show neuropathological alterations. In addition to changes due to secondary or opportunistic infections, there is widespread subcortical white matter pathology with relative sparing of cortical structures. Those diffuse, noninflammatory changes are now subsumed under *HIV leukoencephalopathy*. Microscopic examination also reveals foamy macrophages and multinucleated giant cells invading both white matter and subcortical nuclei, particularly basal ganglia structures. Such focal inflammatory findings are characterized as HIV encephalitis. Also, there may be pathology in the spinal cord associated with paraparesis, particularly vacuolar myelopathy. Insofar as many other patients have significant cognitive deficits in the context of relatively little pathological alterations, it is clear why investigators have encountered difficulty when attempting strict clinical-pathological correlation.

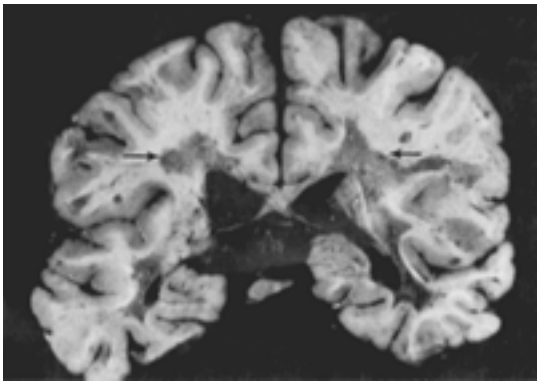
The mechanism by which HIV causes its functional effects remains unknown. Current data point to (1) neurons and supporting cellular structures, through the actions of the virus itself or from its coat proteins; (2) the undesirable effects of activated immune components (such as activated macrophages); and (3) possible excitatory neurotoxic effects of endogenous neurotransmitters that have been dumped into surrounding interstitial fluids (e.g., quinolinic acid affecting glutamate receptor subtypes, leading to the toxic accumulation of intracellular calcium).

The diagnosis of HIV-related neuropsychiatric syndromes requires a high index of suspicion and a sensitivity to possible demographic risk factors, including homosexual behavior, sexual promiscuity, intravenous substance abuse, and sexual relations with high-risk partners. In addition, there is a gradual movement of the HIV virus into the broader heterosexual population. Psychopathological changes may precede frankly defined cognitive abnormalities. The clinician also must be alert to early, subtle intellectual decline: the patient may remain within the normal range on standard neuropsychological tests but may perform at a level lower than was attained previously. In addition to neuropsychological assessment, neuroimaging may demonstrate abnormalities in subcortical periventricular and deep white matter.

AIDS dementia complex has become a major target in pharmacotherapeutic trials to cure or ameliorate the effects of HIV infection. Preventing its emergence or prolonging the time it takes to appear have become possible end points for some studies. Others are considering AIDS dementia complex as a direct target for intervention. Future antiviral pharmacotherapies may be targeted specifically to the brain to eradicate any possible reservoirs of HIV, in a fashion similar to the use of irradiation or antitumor agents in children with leukemia.

**Immune and Autoimmune Disorders** Three broadly defined pathophysiological mechanisms involving the immune system can be associated with neuropsychiatric disorders: (1) hypofunction of the immune system may contribute to infectious diseases and possibly to neoplastic illnesses; (2) definite or putative autoimmune diseases may cause behavioral disturbances by affecting the function of organ systems in a way that compromises brain activity (e.g., the hyperthyroidism of Graves' disease or hepatic failure from primary biliary cirrhosis); (3) autoimmune illnesses may also affect brain function more directly by causing cerebral ischemia due to vasculitis or by direct CNS parenchymal inflammation. Some primary neurological diseases (e.g., multiple sclerosis) may involve autoimmune pathophysiology (Fig. 10-4). A major example of an autoimmune disorder involving the CNS is systemic lupus erythematosus.

**FIGURE 10-4** Multiple sclerosis. Coronal section of cerebral hemispheres showing large, sharply demarcated plaques adjacent to the bodies of the lateral ventricles (arrows). Other plaques are found adjacent to the temporal horns and smaller plaques are present in the subcortical white matter and centra semiovales. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)



Cathy Jarvis, a 25-year-old mother with a 3-year history of systemic lupus erythematosus was admitted to a university hospital in an acute confusional state with inability to maintain attention or to carry on a coherent conversation and with marked disorientation to time and place. Before her hospitalization she had become progressively more confused over a number of days, and had started to believe that the neighbors were watching her. On the day of admission she had run out of her house and into the street in a state of uncontrollable agitation.

On admission to the hospital emergency room, Cathy was given intramuscular haloperidol (Haldol), but by the next morning her clinical picture had worsened dramatically. She was now rigid, mute, uncommunicative, and unresponsive to all questions and she exhibited facial grimacing. Her course fluctuated so that at times she became excited, screamed continuously, and seemed to be responding to auditory and visual hallucinations; at other times she was mute and rigid. She required total nursing care, with intravenous feeding, catheterization, and four-point restraint. She received frequent sedation with lorazepam (Ativan), a short-acting benzodiazepine. Because she was thought to have lupus cerebritis, intravenous methylprednisolone (Depo-Medrol), a steroid, was begun, but there was no improvement in her clinical condition.

During the next 3 weeks Cathy's condition deteriorated. She lost considerable weight, was unable to stand, and continued to require total nursing care. On day 28 she was referred for electroconvulsive therapy (ECT). After seven treatments she gradually responded, sought to feed herself and to stand, was more alert, and recognized her family. Rigidity was now only occasionally present. A lumbar puncture demonstrated the presence of immunoglobulin-G (IgG) antineuronal antibodies in high titer, consistent with a diagnosis of CNS involvement with lupus.

Over the next few weeks periods of lucidity alternated with rigidity, mutism, negativism, and staring. By day 90 of Cathy's hospitalization, a second course of ECT was begun. After 10 treatments, she was verbal, euthymic, and cooperative. (Reprinted with permission from *DSM-IV Casebook*.)

Often lupus is considered in the differential diagnosis of new-onset psychopathological syndromes. Although the etiology of lupus is not known, evidence implicates immunological mechanisms in its pathogenesis. Numerous organ systems may be involved. The disease may affect brain function (thereby producing psychiatric symptoms) indirectly, through such mechanisms as fever, renal failure, or

pulmonary disease. In a minority of patients it may cause pathology directly, most likely from vasculitis affecting cerebral vessels. Patients with CNS disease may experience seizures, transverse myelopathies, or behavioral abnormalities, including delirium, psychotic syndromes, and affective lability. Clinicians evaluating patients with psychiatric symptoms of recent onset (particularly women in the second through fifth decades of life) should carefully consider the medical history, review of systems, physical examination findings, and routine laboratory screens, to look for evidence of systemic organ system involvement. The erythrocyte sedimentation rate (ESR), while nonspecific, is substantially elevated during acute CNS lupus and provides a useful screen. More specific laboratory tests (e.g., antinuclear antibody assay and antibodies to double-stranded deoxyribonucleic acid [DNA]) may be pursued when indicated. Neuroimaging scans may show cerebral infarctions but are often normal early in the disease. Glucocorticoids are the mainstay of treatment for acute CNS systemic lupus erythematosus. Psychotropic medications may be needed to treat specific behavioral symptoms (e.g., antipsychotic agents for severe agitation during delirium).

**Cardiovascular Disease** Because the extremely high metabolic activity of the brain is obligatorily aerobic, the brain is exquisitely sensitive to relatively minor perturbations in blood flow. Thus, alterations in cardiac function ranging from grossly obvious (cardiogenic shock) to relatively subtle (compensated congestive heart failure, chronic low-output states) often manifest with CNS dysfunction. The consequent psychiatric phenomenology may vary due to largely unknown factors, but delirium, dementia, and depressive episodes are especially common. Perfusion failure, depending on its cause, may lead to insidious, gradual changes or dramatic decrements in function. Transient profound drops in blood pressure, typically associated with major cardiac events (including surgery), may lead to mental status alterations that are difficult to pinpoint initially. Clinicians are faced with distinguishing soon-to-remit symptoms, such as postoperative delirium arising from metabolic imbalances, from subtle persisting intellectual and behavioral alterations caused by hypofusion leading to cell death.

Intrinsic cardiac illness, such as mural thrombus or valvular disease, may also be a source of embolic cerebral infarction (Fig. 10-5). Cardiovascular disease may also lead to brain dysfunction by serving as a risk factor for cerebrovascular disease. Identified risk factors for stroke include hypertension, diabetes mellitus, cigarette smoking, atrial fibrillation, left ventricular hypertrophy, and coronary artery disease.

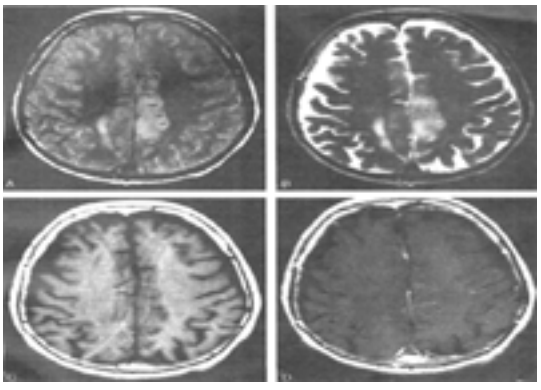


**FIGURE 10-5** Acute cortical infarction. **A** and **B**, Proton-density and T2-weighted axial MRI scans show increased signal intensity within the medial cortex of left frontal and parietal lobes. Note swelling of gray matter and prominence of blood vessels within this lesion. **C** and **D** T1-weighted axial MRI scans before and after gadolinium administration demonstrate several linear foci of contrast enhancement within the area of infarction in the left frontal and parietal lobes, most consistent with enhancing arterial branches. Contrast enhancement of arterial branches is consistent with static blood

flow within the infarct, and generally is seen only within the first few hours to 5 days after the onset of acute infarction. (Reprinted with permission from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, Baltimore, 1995.)

Cerebrovascular disease of any cause and pathophysiology—thrombotic, embolic, or hemorrhagic—will affect brain function. Psychiatric symptoms may develop either suddenly (presumably in relation to abrupt neuronal losses and dysregulation) or gradually (perhaps in relation to cumulative infarcted brain tissue and to longer-term adaptations of neurochemical systems). Table 10-11 presents an overview of the variety of cerebrovascular events.

**Table 10-11** Types of Cerebrovascular Events

Recent data have undercut the long-held notion that vascular disease due to a vascular etiology always progresses in stair-step fashion, as has been described for the course of vascular dementia. Rather, progression appears to vary in rate and form, depending both on the type of vasculature affected (large versus small vessels) and on basic pathobiology (perfusion insufficiency versus occlusive disease).

It is important to recognize that psychiatric phenomena may manifest without other clinical evidence of a neurological event. For example, patients with right parietal infarction have presented with delirium but no other neurological symptoms or signs. Alternatively, an infarction in the distribution of the left middle cerebral artery may cause Wernicke's aphasia, characterized by fluent paraphasic or jargon-filled speech, poor comprehension and repetition, and suspicious or aggressive behavioral responses. No other signs of cerebral disease may be evident, and such patients have been misdiagnosed as having paranoid schizophrenia. It is also important to understand that pathology does not specify phenomenology. For example, patients with multiple infarcts on MRI are often labeled as having vascular dementia; however, multiple infarctions may manifest with dementia, with other behavioral syndromes (mood disorder, psychosis, anxiety, personality change), or with no definable neuropsychiatric syndrome.

**Congenital and Hereditary Conditions** Patients with congenital and hereditary conditions often present for psychiatric evaluation because of the frequency of associated behavioral disturbances.

A 15-year-old boy was brought to the emergency room by his mother, who, clutching the on-call resident's arm, pleaded, “You've got to admit him; I just can't take it anymore.” The patient had been brought home from a special school by his mother 6 months previously. The mother showed the resident papers from the school that indicated that the patient's IQ was 45. He had had several placements, beginning at age 8. On visiting days, the boy always pleaded with his mother, “Mommy, take me home.” After a year or so away, the patient would be brought home by his mother, who had always been wracked by guilt because of his retardation and her inability to manage him in the home. The patient was an only child whose parents had been divorced for the past 4 years. The father had moved to another city.

During the last 6 months at home, the patient had increasingly become a behavior problem. He was about 5'9" tall and weighed almost 200 pounds. He had become destructive of property at home—breaking dishes and a chair during angry tantrums—and, more recently, physically aggressive. He had hit his mother on the arm and shoulder during a recent scuffle that began when she tried to get him to stop banging a broom on the apartment floor. The mother showed her bruises to the resident and threatened to call the mayor's office if the hospital refused to admit her son.

On examination, the boy was observed to have the typical signs of Down syndrome, including thick facial features, slightly protruding tongue, epicanthic fold of the eyelids, and simian crease of the palms of the hands. With indistinct and slurred speech, the boy insisted that he “didn't mean to hurt anybody.” (Reprinted with permission from *DSM-IV Casebook*.)

Congenital and hereditary conditions are of great significance in the understanding of brain-behavior relationships because they are often seen in biologically homogeneous populations with relatively specific behavioral and neuropsychiatric syndromes. Congenital conditions are caused either by genetic abnormalities affecting autosomes, sex chromosomes, or single genes or by fetal insults during the prenatal, perinatal, or immediate postnatal periods. Table 10-12 lists several developmental and hereditary disorders with significant neuropsychiatric manifestations. In DSM-IV these conditions are classified according to the age at which symptoms manifest, what symptoms are present, and whether the symptoms are progressive or static.

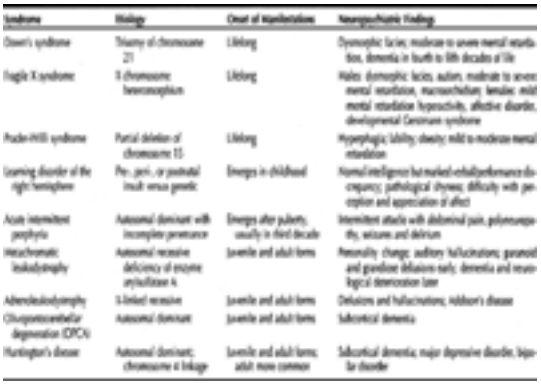


**Table 10-12** Examples of Developmental and Hereditary Disorders With Neuropsychiatric Manifestations

**Down Syndrome** Down syndrome results in static phenotypic abnormalities, including characteristic facies and mental retardation, and has been associated with a progressive decline in functioning beginning in the third or fourth decade of life. Alzheimerlike pathological changes are frequently detected at autopsy, even in patients who did not exhibit functional decline before death.

**Fragile X Syndrome** Fragile X syndrome is the second most common cause of mental retardation in men and one of the few known causes of the autism syndrome. Female heterozygotes also manifest significant psychiatric pathology, including mood disorders, difficulties with behavioral control, and a neuropsychological profile of dyscalculia, right-left disorientation, and constructional dyspraxia similar to the Gerstmann syndrome, described in patients with acquired lesions in the dominant parietal lobe. Learning disorders usually become obvious when the child begins school.

**Huntington's Disease** *Huntington's disease*, also known as *Huntington's chorea*, has been the focus of intensive neuropsychiatric, genetic, and pharmacological research since the 1970s. First described by George Huntington on Long Island in 1872, the disorder has received intense scrutiny, and its site on chromosome 4 has been determined. The disorder is related to an unstable trinucleotide repeat (CAG), associated with more than 36 copies of the specific sequence. Onset typically occurs in middle life, usually between ages 25 and 50 years. The juvenile form, with onset occurring during adolescence, is somewhat different phenomenologically, with a greater degree of dystonia early in the disease process and a faster rate of disease progression. A greater number of CAG trinucleotide repeats is associated with an earlier age of onset of clinical disease. Lower cognitive performance is detectable in those clinically asymptomatic at-risk individuals who have greater numbers of repeats. A greater number of repeats is associated with more severe neuronal loss in both caudate and putamen at postmortem examination, and perhaps a faster rate of pathological deterioration. Although the exact neurobiological role of the abnormal protein (*huntingtin*) encoded in Huntington's disease remains unknown, other findings point to defects in mitochondrial energetics as a possible contributing mechanism.

Huntington's disease is not diagnosed formally until the typical movements appear, although both psychiatric and neuropsychological manifestations may precede the emergence of motor abnormalities. The psychopathology associated with Huntington's disease has a wide range of manifestations, commonly including affective presentations (typically depression, but mania as well); psychoses, often with a schizophrenic appearance; personality changes, and anxiety disorders. Some individuals, however, may proceed through the entire course of the illness with no evident psychopathology. Often the psychopathology is most florid during the early and middle stages of the disease, but as the characteristic subcortical dementia proceeds patients begin to exhibit less characteristic behavior and thus appear less symptomatic. The suicide rate is higher in patients with Huntington's disease than in the general population but suicidal ideation may be difficult to detect because patients tend to be less spontaneous and forthcoming as a result of the cognitive difficulties associated with the disorder. Interviewers must take an active or probing approach; patients who quickly pass off inquiries when presented with open-ended questions may provide more information when queried with specifically structured interview methods.

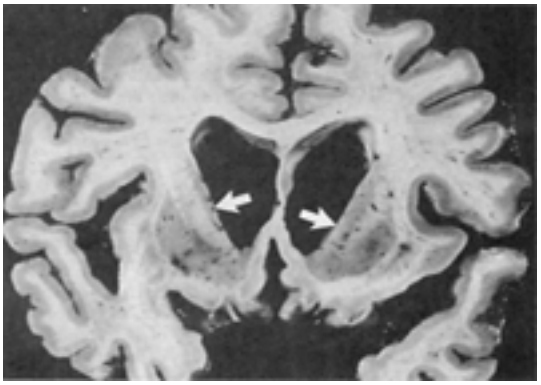
The cognitive disorder of Huntington's disease is more consistent in its presentation than the psychopathological picture, although it too evolves over the course of the disorder. Patients usually experience mild memory difficulties, and the first symptoms may be subtle problems with organizing, planning, and sequencing. Spontaneity and verbal elaboration may be diminished relatively early, although that appears to be somewhat more variable in its time of onset. As the disease progresses, psychomotor slowing progresses relatively rapidly, with concomitant difficulty with complex tasks, while recall of old knowledge and factual information remains less affected. Unlike patients with dementia of the Alzheimer's type, many patients with Huntington's disease remain insightful long into the course of their disease. Thus, their mood disturbances and potential suicidality may be tied in part to a clear realization of their situation. Indeed, even as patients respond to standard antidepressant therapy with enhanced sleep, energy, appetite, and improved overall mood state, they may remain realistically pessimistic about their long-term situation.

Patients with Huntington's disease begin to develop an apathetic appearance as the disease progresses. Early in the course, they continue to show interest and responsiveness when presented with structured situations in which they can take part; frank apathy and disinterest develop later and persist even in the context of prompted or structured assistance. Although some degree of verbal learning impairment is an early feature of the dementia, it is more prominent later in the disease course. Similarly, subtle visuospatial processing problems may occur early but do not become prominent clinically until later.

Just as the cognitive disturbance of Huntington's disease evolves slowly, so too there is a gradual change in the associated movement disorder. In most affected adults the movement disorder is typically choreiform at the outset but becomes more dystonic and bradykinetic as the disease progresses. Toward the end of the disease course, patients are bedridden, mute, and overcome by a severe dystonic state.

The pathology and neurobiology of Huntington's disease have been studied intensively in recent years (Fig. 10-6). The striatum bears the brunt of the pathology, with interruption of crucial corticostriatothalamocortical relays. Although there are no immediate, reciprocal corticostriatal connections, that multineuronal pathway similarly modulates motor function, cognition, and perhaps mood. Recent theories suggest abnormal function of excitatory neurotransmitters, most apparently acting on glutamate receptors, that serve as endogenous neurotoxins. Although efforts have been made to use symptomatic pharmacological treatments for both the psychiatric and motor symptoms, more recent pharmacotherapeutic trials have aimed at preventing progression of the disease by employing potential glutamate receptor blockers. Such efforts have provided models for similar therapeutic approaches to Parkinson's disease and Alzheimer's disease.

**FIGURE 10-6** Huntington's chorea. There is marked atrophy of the caudate nuclei (arrows) and mild dilatation of the lateral ventricles. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)



The mood disorders associated with Huntington's disease have proved amenable to symptomatic treatments. Standard doses of antidepressant medications may be needed, although patients often respond sensitively to rapid changes in medication and experience unwanted adverse effects. ECT has been beneficial for severe major depressive symptoms, especially in high-risk suicidal patients. The schizophrenia-like presentations of Huntington's disease appear less responsive to antipsychotic therapy than phenomenologically similar idiopathic disturbances. Patients with Huntington's–disease–related anxiety disorders have shown sufficient benefit from available medication regimens to warrant empirical trials. Psychotherapy, usually with the patient and family treated together, may lead to substantial therapeutic gains. Clinician commitment to the long haul may prove especially reassuring and stabilizing.

Like other hereditary neuropsychiatric disorders, Huntington's disease illustrates the need for all psychiatric evaluations to include a careful documentation of family history. Patients with Huntington's disease may present with mood or psychotic disturbances and no apparent abnormal involuntary movements and may be treated symptomatically with pharmacotherapeutic agents, only to evince the characteristic motor disorder later. Ignorance of the family history has led some to misinterpret that progression as evidence of tardive dyskinesia. The patient may remain incorrectly diagnosed until cognitive impairment becomes unmistakable. In the meantime, patients and families have lost the opportunity to clarify their life plans and develop support for future needs. Psychiatrists must remain vigilant in taking the family history whenever evaluating a new patient.

**Other Conditions** Learning disorders involving left hemisphere functions such as reading, writing, or mathematics are well known clinically. A learning disorder of the right hemisphere has been described that is characterized by intact linguistic and academic skills; left-sided soft (nonlocalizing) neurological signs; and profound impairments in functions dependent on the right hemisphere, including visuospatial skills, modulation of affect, and the paralinguistic aspects of communication. The etiology of the learning disorder is unknown, although a retrospective history of prenatal or perinatal insults is common, as is a family history of similar impairments. Acute intermittent porphyria is a hereditary disorder that is intermittent. In between episodic attacks, most patients maintain normal development. The leukodystrophies and degenerative hereditary disorders listed in Table 10-12 can produce symptoms during childhood or not until adulthood. Development until the appearance of symptoms is normal. However, in each of these disorders psychiatric symptomatology can precede other evidence of the disease process and lead to an erroneous diagnosis of an idiopathic psychiatric disorder.

**Physiological Disorders—Epilepsy** Epilepsy is the prototype of a physiological disease process that manifests psychiatric symptoms. It has long held the interest of neuropsychiatry and has been studied intensively, if not always fruitfully. The complexities of defining brain-behavior relationships in epilepsy merit extended discussion.

**Definition** Epilepsy is defined as a condition of recurrent seizures due to CNS disease or dysfunction. Seizures are behavioral alterations of abrupt onset and termination that are associated with sudden electrical discharges of the brain. Although the essential paroxysmal form remains constant and in fact defines a seizure, the content of the behavioral disturbance can vary widely. Seizures can be generally classified into two broad categories, generalized and focal. In generalized seizures the electrical abnormality usually originates from subcortical structures (primarily the brainstem) and then spreads simultaneously to all areas of the cortex. Loss of consciousness is invariable, and the seizure phenomenology is symmetrical and bilateral. Focal seizures originate from a specific brain locality, usually the temporal lobe. The abnormal electrical discharge may remain at the site of origin, proceed gradually to adjacent areas, or spread to include the entire cortex (secondary generalization). The clinical phenomenology of a focal seizure depends on the site from which that seizure originates and may be unilateral and restricted to a particular muscle group, sensation, affect, and so on. The epilepsies are classified based on the type of seizure and the inferred anatomical substrate (Table 10-13). Seizure type and phenomenology are usually constant within the course of a particular patient's disorder. The stereotyped presentation is a major feature of evaluation, diagnosis, and assessment of treatment efficacy.

| |
|---|
| Primary generalized epilepsy |
| Tonic-clonic (grand mal) |
| Absence (petit mal) |
| Myoclonic |
| Other |
| Partial (focal) epilepsy |
| Simple (elementary) symptomatology |
| Focal motor |
| Focal sensory |
| Vegetative |
| Mixed |
| Complex symptomatology |
| Partial complex (psychomotor) |
| Secondary generalized |
| Unclassifiable |

**Table 10-13** Classification of the Epilepsies

**Clinical Features** Seizures can proceed in stages and may include a prodrome, aura, ictus, and a postictal period. Psychopathology may manifest during any of these stages as well as during the interictal (between-seizure) period (Fig. 10-7). A prodrome can be seen in generalized epilepsy, although it is more common in focal epilepsy, particularly temporal lobe epilepsy. A prodrome may consist of irritability, apprehension, sullenness, or a sense of discomfort or disease that builds up gradually over hours to days before a seizure. The prodromal state remits abruptly with the onset of the seizure. The pathophysiological basis for the prodromal state is unknown.

**FIGURE 10-7** Progression of phases in epileptic seizure disorders.

Auras are focal seizures or the initial focal onset of a seizure and are associated with definable abnormal electrical discharges. Auras are abrupt in onset, last for seconds to minutes, may progress to a generalized seizure, or may terminate as the seizure ends. The type of clinical phenomenon depends on the site of origin and can include motor, sensory, autonomic, perceptual, cognitive, and affective abnormalities. Table 10-14 lists a number of common clinical manifestations of auras or focal seizures based on the anatomical site of origin. The auras accompanying seizures originating in the temporal lobe are the most varied. In general, auras may comprise a variety of symptoms and may have unique, individual-specific features, such as the crying out of a particular phrase in a particular language. Despite the great variety of auras, in any individual auras tend to be stereotyped and consistent from seizure to seizure.

| | |
|---|---|
| Sensory | Cognitive |
| Headache | Transient dysphasia |
| Focal pain | Speech automatisms |
| Paresthesia | Subjective confusion |
| Motor | Obsessional thinking |
| Nystagmus | Thought blocking |
| Head turning | Distortion of time sense |
| Scanning | Affective |
| Posturing | Fear |
| Stuttering | Anxiety |
| Autonomic | Sadness |
| Facial flushing | Embarrassment |
| Hot flashes | Placidity |
| Pallor | Guilt |
| Dizziness | Anger |
| Chest pain | Joy |
| Tinnitus | Elation |
| Perceptual | Other |
| Micropsia, macropsia | Genital sensations |
| Heightened auditory acuity | Sexual behaviors |
| Derealization, depersonalization | |
| Déjà vu, *jamais vu* | |
| Hallucinations (visual, auditory, olfactory, gustatory, and tactile) | |

**Table 10-14** Neuropsychiatric Manifestations (in the Aura and Ictus) of Focal Epilepsy

The *ictus*, the epileptic attack, may be generalized or focal. *Primary generalized tonic-clonic epilepsy (grand mal epilepsy)* is characterized by a behavioral arrest or sudden loss of consciousness. This is followed by tonic extension of the upper and lower extremities, then clonic, rhythmic jerking of the extremities. The jerking gradually decreases in frequency, leading to muscle flaccidity. The total duration of the ictus is usually 2 to 5 minutes. Associated features may include urinary and bowel incontinence, sweating, and tachycardia. Generalized absence or petit mal epilepsy is characterized by brief lapses of consciousness lasting 3 to 30 seconds. There are no associated tonic-clonic movements, nor is there loss of postural tone. There may be a slight rhythmical twitching of the mouth. Seizures can occur numerous times during the day. Absence seizures are common and occur primarily in children ages 4 to 12 years. In both types of generalized epilepsies there is amnesia for the epileptic event. Myoclonic epilepsy is characterized by nonrhythmic, brief jerks of the limbs, trunk, and head.

Myoclonic jerks are asynchronous, with body parts jerking at different times and in different sequences, and there is no loss of consciousness. Myoclonic epilepsy is frequently of familial etiology, although it may be associated with brain injury or systemic disease that affects brain function, such as chronic renal disease or hepatic insufficiency.

Partial or focal seizures are distinguished by their localized site of origin. The symptomatology can be simple (elementary) or complex, with the latter characterized by some degree of impairment of consciousness. Partial seizures with elementary symptomatology include focal motor symptoms, focal sensory symptoms, autonomic symptoms, or mixed symptomatology; consciousness is retained throughout the episode, although the seizure discharges can spread to other areas of the brain (jacksonian march) and can also develop into a generalized seizure (secondary generalization). The postictal period may be characterized by a residual focal deficit, such as motor weakness (Todd's paralysis) or dysphasia. Secondary generalization may occur rapidly, giving the false impression of an immediate generalized seizure; videotaped monitoring with simultaneous EEG may be necessary for differentiation.

Partial complex seizures, also known as psychomotor seizures, temporal lobe seizures, or temporal-limbic seizures, are perhaps of greatest interest to psychiatry. The great majority of partial complex seizures originate in the temporal lobes, but the frontal lobes and other sites have also been recorded as seizure foci. The range of presenting symptomatology varies from patient to patient and may include a broad spectrum of disturbances in behavior, cognition, and affect. Auras are frequent in partial complex seizures, representing the focal onset, and it may be difficult to distinguish the aura from the ictus. They are generally associated with clouding of consciousness but retention of posture and muscle tone. The patient may exhibit simple or complex movements, such as pulling on clothing, buttoning or unbuttoning clothing, purposeless hand movements, and fumbling with objects, or may continue with the behavior initiated prior to the seizure, such as closing a window. There may be staring, lip smacking, and wandering. The actual ictus cannot be distinguished from the aura.

Psychiatrists should be familiar with the range of symptomatology associated with partial complex or temporal lobe epilepsy because that disorder is an important diagnostic consideration in adult patients presenting with the new onset of behavioral disturbances. In light of the protean possible manifestations of partial complex epilepsy, the physician must keep in mind that there is a general consistency to the form of partial complex seizures: They have a definite and observable onset and termination; they are always associated with impairment in consciousness, such as confusion or inability to perform cognitive tasks; and they are relatively stereotyped for an individual from episode to episode.

The postictal period may also be characterized by severe disturbances of behavior. Primary generalized tonic-clonic seizures are usually followed by a period of sleep, sometimes headache, and nausea. Focal or partial seizures may have residual focal deficits of varying duration. In partial complex seizures, recovery of consciousness may lag behind recovery of motor function. Frequently automatic behavior, such as repetitive mouth movements, arm movements, and pacing, can be observed. As the postictal period is essentially a delirious state, confusion and cognitive impairment remain. Any disturbance of mood is possible, including anger, lovingness, and the epileptic furor (random, typically nondirected

displays of violence and property destruction). The postictal period usually lasts only minutes, although it may last hours to days. A very rare but disturbing psychiatric postictal complication has been termed subacute postictal aggression. This is associated with directed violence that occurs in well-documented cases of epilepsy, where a patient stereotypically becomes increasingly psychotic, paranoid, and combative following a bout of uncontrolled seizures. Treatment requires both anticonvulsant and antipsychotic medications, although reported cases have occurred in patients who have poorly controlled epilepsy.

**Course** Epilepsy has an annual incidence of approximately 20 to 50 new cases per 100,000 population. The prevalence is 0.2 to 1.0 percent. The majority of cases of epilepsy in patients older than 15 years are of the partial or focal type. Only approximately 25 percent of adolescents or adults over the age of 15 years with seizures have generalized epilepsy. Seizures with onset in childhood are more commonly generalized, particularly absence seizures. Primary generalized tonic-clonic seizures usually occur for the first time before the age of 35 years, although they can occur at any age; absence seizures usually first manifest between the ages of 4 and 12 years. Focal seizures also have their onset commonly before the age of 20 years.

The natural history of seizure disorders has not been defined clearly. Up to one third of all seizures may remit spontaneously without treatment. Absence seizures are generally outgrown by the age of 20 years, although many patients do develop another form of generalized epilepsy as adults.

The etiological considerations for seizures vary with the age at onset. Early-onset epilepsy is usually a concomitant of genetic factors or an insult to the developing neural system in utero or in childhood; the latter can include trauma, infections, or toxic exposures. For seizures starting in adulthood, the etiological considerations include alcohol or drug withdrawal, trauma, infection, and tumors. The tumors are the primary causes of seizure disorders during the middle adult years; cerebrovascular disease is the most common etiology among the elderly.

**Treatment** Anticonvulsant pharmacotherapy first developed empirically, without specific knowledge of either the pathophysiology of seizures or the neurochemical mechanisms of therapeutic agents. Although the primary prescribed anticonvulsants (carbamazepine [Tegretol], phenytoin [Dilantin], valproic acid [Depakene], and phenobarbital) have remained consistent since the 1980s, recent years have seen the rapid emergence of new compounds (Table 10-15). Most medications work through one of three mechanisms of action: potentiation of γ-aminobutyric acid (GABA)-mediated neuronal inhibition, inhibition of glutamate-mediated excitatory postsynaptic receptors, or control of sodium and calcium voltage-gated ion channels; Table 10-16 summarizes these actions. It is particularly important to note that anticonvulsant medications have proven to be a fruitful source of novel psychiatric compounds.

**Table 10-15** Chronology* of Antiepileptic Drugs

| | |
|---|---|
| Conventional Drugs | |
| Phenobarbital | 1912 |
| Phenytoin | 1938 |
| Trimethadione | 1946 |
| Phensuximide | 1953 |
| Methsuximide | 1957 |
| Ethosuximide | 1960 |
| Benzodiazepines | 1965 |
| Carbamazepine | 1974 |
| Valproate | 1978 |
| New Drugs* | |
| Felbamate | 1993 |
| Gabapentin | 1994 |
| Lamotrigine | 1995 |
| Topiramate | 1997 |
| Tiagabine | 1997 |
| Vigabatrin | In Europe |
| Oxcarbazepine | In Europe |
| Loreclezole | In trials |
| Stiripentol | In trials |
| Zonisamide | In trials |

* Dates refer to U.S. introduction; lamotrigine was marketed earlier in Europe.
Adapted from Avoli M: Molecular mechanisms of antiepileptic drugs. Sci Med 4(4):58, 1997.

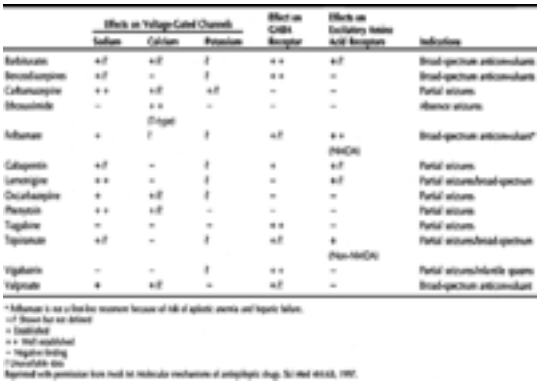


**Table 10-16** Antiepileptic Drugs

**Psychopathology** Psychopathology, namely disturbances in behavior, cognition, perception, or mood, can occur at any point in the seizure process. The prodrome may be characterized by a sense of irritability or apprehension. Families often report that they know when a relative is going to have a seizure on the basis of a change in temperament or disposition. Auras may include a variety of psychopathology, including dissociative experiences, hallucinations in all spheres, derealization, depersonalization, and disturbances of mood or affect. The disturbances of mood, such as a subjective sense of fear, anxiety, or depression, can be distinguished from normal expressions of the same emotion in that generally they are more crude, stereotyped, and brief emotional states. Joy, elation, or euphoria is less common. Ictal states can manifest striking changes in behavior that are likely to be coarse and disorganized. The list of ictal manifestations in Table 10-14 includes a variety of hallucinations and dissociative experiences, as well as sudden and unpredictable shifts in mood. Other sensory or psychic experiences can occur out of their usual context (a classic case is that of a woman who had spontaneous orgasms in church). The postictal state is a delirium that can display the full range of disturbances in level of arousal, ranging from stupor to hypervigilance. Partial seizures may be followed by a milder delirium that is detectable only from disorganization in behavior or difficulty with simple cognitive tasks such as registration and repetition. The issue of interictal psychopathology has been much studied and debated, in general, the psychiatric symptomatology associated with the prodrome, aura, ictus, and postictal state is remarkably broad—virtually any thought, feeling, movement, or perception that the brain can produce may be seen. The clinician must be attentive to the form and course of these symptoms whenever considering epilepsy as a possible etiological explanation for abnormal behavior.

**Violence and Aggression** The issue of violence or aggression as a neuropsychiatric manifestation of an

ictus has provoked much controversy. In the legal arena epilepsy is occasionally invoked as a defense to mitigate culpability for a violent or even murderous act. Irritability or agitation can be a component of the prodrome, the aura and ictus can encompass angry affect and striking out, and the postictal state can manifest with fear and confusion with intact motor function. Although this might suggest the possibility of violent acts as a component of seizures, there is limited potential for such actions. Automatic acts of violence during epileptic seizures are short-lived, fragmentary, undirected, and most often occur in response to actions (such as attempts at restraint) that provoke or irritate the seizing individual. Examples include spitting, swearing, and striking out in a flailing fashion. For violence to be considered a manifestation of epilepsy, it must conform to the known temporal sequence and symptomatology of a seizure; namely, there must be a clear onset and termination, together with other clinical signs (e.g., confusion, incontinence, and impairment of consciousness) and stereotypy. A special 1981 epilepsy task force of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), after studying videotapes of selected violent patients with epilepsy, recommended criteria to determine if a particular act of violence is ictal: (1) a clear diagnosis of epilepsy; (2) documented automatisms, preferably on videotape; (3) documented aggression during the automatisms that corresponds to an EEG-proved ictus; (4) demonstration that the aggressive act is characteristic of the patient's usual seizure form; and (5) clinical consensus that the act was related to the actual seizure.

People with epilepsy have long been thought to display psychopathology during the interictal period as well. Epilepsy was thought to be a subtype or complication of insanity, and so was included in most psychiatric nosologies of the past two centuries. Epilepsy patients typically were housed in asylums for the insane. In 1791 Philippe Pinel included among his recommendations for asylums the suggestion that other patients be shielded from epilepsy patients because of their “almost always incurable” status and his sense that “few objects are found to inspire so much horror and repugnance . . . than the sight of epileptic fits.” Griesinger stated that “a very great number of epileptics are in a state of chronic mental disease even during the intervals between the attacks.” Interictal psychopathology can be grouped into psychotic disorders, mood disorders, personality abnormalities, cognitive disorders, and secondary repercussions.

**Psychotic Disorders** Jean Etienne Esquirol, in his 1845 description of female institutionalized epilepsy patients, reported frequent psychotic symptoms, including hallucinations in all spheres:

> They have hallucinations most varied . . . they think they see luminous bodies by which they fear they might be embraced . . . they smell odors the most fetid . . . they hear sounds like the bursting of a thunderbolt, the roll of drums, the clash of arms in the din of combat.

Karl Jaspers, in *General Psychopathology*, classified epilepsy as one of the three major psychoses, along with schizophrenia and manic-depressive illness. He defined *genuine epilepsy* as “convulsive disorders which are not due to any known somatic process.” Numerous studies have evaluated psychosis among epilepsy patients; unfortunately, most have been hampered by the lack of clear or standardized definitions for the symptoms being investigated. In addition, many studies have not distinguished between psychosis occurring in the context of the ictus, the prodrome, or the postictal state, and many have not indicated whether such symptoms were detected specifically during periods of

interictal electrical stability. Few studies have discriminated between symptoms occurring in clear consciousness versus those occurring coincident with impaired consciousness. Nonetheless, clinicians generally encounter a higher incidence of psychosis among epilepsy patients, particularly those with temporal lobe foci, than in the general population. Some studies have specifically referred to paranoid ideation, delusions, ideas of reference, visual hallucinations, and first-rank auditory hallucinations as being common. In 1963 Eliot Slater and A.W. Beard identified an atypical schizophrenia, characterized by visual and auditory hallucinations, ideas of reference, and persecutory delusions, occurring in the context of preservation of affect and a level of social adaptation better than that of comparably psychotic schizophrenia patients. They further noted that the psychotic symptoms did not occur until many years after the onset of seizures (a mean of 14 years) and then occurred with an apparent periodicity. The occurrence of the psychotic episodes was unrelated both to the frequency of seizures and to measured anticonvulsant efficacy.

Although the true incidence or prevalence of psychotic disorders in epilepsy patients is unknown, there is general consensus that the psychotic disorder seen in epilepsy is distinct in form from idiopathic psychiatric diseases and is characterized by the features described by Slater and Beard. Other associated findings may include an association between psychosis and left hemispheric seizure focus (especially in the temporal lobe), female sex, sinistrality, or tissue abnormality (alien tissue, such as hamartomas or focal dysplasia, is more commonly found at autopsy or after surgical excision in the psychotic patients). These psychotic disturbances have been referred to as the schizophrenia-like psychosis of epilepsy and the interictal psychosis of epilepsy. Standard antipsychotic medications are beneficial symptomatically but not as efficacious as in idiopathic psychotic disorders. Some studies have noted marked improvement in the psychotic symptoms with improved seizure control following either pharmacotherapy or surgical excision of the seizure focus. A smaller number of studies have reported an increase in psychotic symptoms occurring with improved seizure control, prompting a theory of antagonism between symptoms of psychosis and seizure control.

The observation of a consistent psychotic disorder of increased prevalence in epilepsy patients has led to an intense search for the underlying mechanism in the hope of describing a more general explanation for psychotic processes. Three hypothetical mechanisms for interictal psychoses have been advanced. The first hypothesis suggests that the schizophrenia-like illness in epilepsy is epileptic in origin or related to abnormal electrical brain discharges. Kindling, an experimental animal model for the spread of epileptic foci, has been suggested as a paradigm for the development of psychosis in epilepsy. Chronic stimulation of the brain in animals can lower the electrical threshold for the development of electrical or clinical seizures. Over time, abnormal discharges develop at previously subthreshold levels of stimulation or even spontaneously. Abnormal behaviors associated with these experimentally induced brain discharges can also persist, even after stimulation has ceased and there are no motoric convulsions. It has been suggested that human kindling occurs at various brain foci, particularly the temporolimbic structures, resulting in psychotic and behavioral disturbances that may manifest only after years of seizure activity.

A second hypothesis for the development of interictal psychosis focuses on a proposed antagonistic relationship between seizure frequency (or, more accurately, EEG abnormality) and psychotic symptoms: forced normalization is the putative process by which a psychosis of sudden onset can manifest with the achievement of seizure control and associated with a normal cortical EEG. Studies of forced normalization have primarily involved case reports, and findings have been difficult to replicate. Clinical treatment regimens based on the antagonism theory, such as allowing episodic seizures or performing ECT on psychotic epilepsy patients, have proved ineffective, further weakening that proposal.

A third hypothesis to explain interictal psychosis suggests that it may not be related specifically to abnormal electrical activity but may instead reflect a common brain dysfunction that causes both epilepsy and psychosis. This hypothesis stresses the dysfunctional or broken brain inferred in epilepsy and regards the psychotic disorder as yet another symptomatic manifestation. Recent quantitative brain-imaging studies in epilepsy patients with psychotic disorders have not revealed consistent structural abnormalities within that patient group. However, specific symptom correlations have been reported, among them an increased frequency of temporal lobe structural abnormalities in epilepsy patients with auditory hallucinations. Similar findings associating specific psychotic symptoms with defined cerebral abnormalities have also been reported in other psychiatric conditions (e.g., schizophrenia). Further symptom-based research utilizing imaging and physiologically sensitive techniques may better delineate the brain regions where dysfunction can lead to particular psychotic symptoms.

**Mood Disorders** Affective changes can occur as part of the seizure prodrome, aura, ictus, or postictal state. Irritability is a common prodromal manifestation. Temporal lobe auras may be accompanied by mood abnormalities, most commonly fear and anxiety, although a depressive affect is possible and, more rarely, elation or euphoria. Descriptions of postictal sadness are common. All of those affective changes are generally brief, lasting minutes to hours. They differ from normally experienced vacillations in mood, in that they occur independent of any particular context, and from the pervasive and enduring affective changes found in primary mood disorders.

Mood disorders in the interictal period have not been studied as comprehensively as psychotic or personality disorders. Many authors have noted that epilepsy patients have a strong tendency to endorse items of sadness and anxiety on self-report inventories. Few studies have used clinical examinations or standardized interviews to determine the presence of mood disorders such as major depressive disorder or bipolar I disorder. One study of epilepsy patients diagnosed with major depressive disorder found that at least half of the patients had family histories of mood disorder and that no clear relation existed between severity of depression and seizure type, seizure frequency, seizure focus, or age at seizure onset. Although definitive studies of the incidence and prevalence of clinically defined mood disorders in epilepsy are needed, there is less support overall (compared with psychosis) for an elevated prevalence of mood disorders in epilepsy patient populations. Many patients do express persisting dysphoria, perhaps reflecting the dissatisfaction and maladjustment associated with a chronic disease.

Regardless of the cause of the dysphoria or dissatisfaction in epilepsy patients, there is an increased prevalence of suicide attempts and completed suicides. The incidence of suicide in patients with epilepsy

is fivefold greater than in the general population. In patients with temporal lobe epilepsy the incidence of suicide increases to 25 times that of the general population, but the underlying psychopathology remains to be defined.

**Personality Change** There has been a long-standing misperception that an epileptic personality is distinguishable and common. Esquirol noted in his studies of 385 female epilepsy patients that "only one fifth were free from intellectual derangement, but nearly all of these were irritable, peculiar, and easily enraged." Griesinger commented on the "dominant, suspicious, discontented, misanthropic perversion of sentiment . . . observed in many epileptics." Eugen Bleuler spoke of the "epileptic excess of emotion . . . easily aroused, remarkably persistent . . . difficulty in abandoning any particular thought . . . fixation to a single theme . . . precise attention to detail." Karl Jaspers described "viscosity, slowing down, explosiveness and dementia" as characteristic of epilepsy patients. These characterizations were frequently based on chronically institutionalized patient populations representing a selection of the most severely impaired patients, in whom the effects of brain injury (especially related to repeated seizures, status epilepticus, and recurrent hypoxia), the deprivations of institutionalization, and toxic treatments undoubtedly confounded clinical observation. More recent attempts at detecting a recognizable, diagnosable personality disorder in community samples of epilepsy patients resulted neither in the description of a discrete personality syndrome nor in a higher prevalence of known personality disorders.

Because standard personality inventories have not uncovered specific abnormalities in epilepsy patients some researchers have focused on particular traits or behaviors. An interictal behavior syndrome of temporal lobe epilepsy has been described that encompasses four traits or behaviors: (1) altered sexuality, usually a decreased interest in sexual matters but at times involving hypersexuality or deviant sexual interests; (2) hyperreligiosity, described as an unusually deepened interest in moral affairs and matters of global importance, with vivid case descriptions of multiple religious conversions and intrusive polemicizing; (3) hypergraphia, with patients maintaining voluminous writings, including journals, essays, and novels; and (4) viscosity or stickiness, a characteristic described for more than a century, including a preoccupation with detail, digressive or overly inclusive speech, and resulting impairments in social discourse.

Although the literature supporting such a personality syndrome is rich with clinical case histories, systematic study to define such a syndrome has been difficult to replicate. Investigators using an 18-point inventory of those behaviors found they could not distinguish patients with epilepsy from other psychiatric populations or patients with temporal lobe epilepsy from those with generalized epilepsy. Thus, the bulk of data suggests that the clinical complex of overinclusiveness in speech, interpersonal action, and writing; alteration of sexuality; and intensified emotion and cognition (hypercosmiscity) is rare and not specific for temporal lobe epilepsy. However, isolated features of this cluster may be more common among patients with temporal lobe epilepsy. When the entire picture is encountered clinically in the absence of a readily apparent seizure disorder, the clinician may wish to pursue a more intensive evaluation if the patient fails to respond to standard psychiatric therapies.

**Cognitive Disorders** An early view of epilepsy considered it a degenerative disorder with a progressive deterioration in cognition, similar to that seen in the degenerative dementias. Modern prospective

studies, however, have disproved this belief and have demonstrated no progressive decline in cognitive skills in a general population of epilepsy patients. A subpopulation of patients with epilepsy does demonstrate a lower intelligence quotient (I.Q.) spread than the normal distribution. This probably results from a combination of factors, including the original brain damage or dysfunction responsible for the epilepsy, occasional disruption attributable to the seizure disorder, and drug effects. Numerous anticonvulsants, including ethosuximide (Zarontin), phenytoin, phenobarbital (Solfoton), and carbamazepine, have been demonstrated to lower performance on tasks of concentration, memory, and motor speed; motor speed is least impaired.) Epileptic dementia, while certainly uncommon, has been described in patients with defined CNS lesions or uncontrolled seizures. It probably reflects the cumulative effect of frequent seizure-induced hypoxic episodes and perhaps toxicity from long-standing treatment with high dosages of anticonvulsants. Phenytoin, in particular, has been demonstrated to cause cerebellar degeneration with long-term use.

**Behavioral and Secondary Repercussions** Despite a less glamorous research appeal, the more compelling and clinically demanding aspects of interictal function may be the behavioral, interpersonal, and social problems arising from irritability, agitation, or aggression. There are no well-defined, systematic, or tested approaches to treating those behavioral difficulties when they arise. It was long believed that maladaptive behavior, particularly aggressive behavior, as characterized by physical assaultiveness, destructiveness, and self-injury, was more common in patients with epilepsy. Recent methodologically rigorous studies, however, demonstrated that maladaptive behavior does not correlate with the presence of epilepsy when epilepsy populations are compared with appropriately matched controls. Maladaptive behavior is, however, related to the overall extent of brain damage in both types of populations. This important point cannot be overemphasized: Epilepsy is a florid manifestation of a physiologically abnormal brain, and in most instances, the fundamental CNS dysfunction that causes seizures also causes associated neuropsychiatric abnormalities.

Especially among severely afflicted epilepsy patients, obstacles to effective social functioning and personal autonomy pose the greatest therapeutic challenges for clinicians and families. Patients may not receive adequate education because seizures may interfere with daily school attendance. Patients may be restricted from many occupations owing to employers' fears of patients sustaining injury in the workplace. Limitations on driving can markedly diminish the independent functioning of these individuals and many patients are compelled to remain dependent on family, even into adulthood.

**Pseudoseizures** Pseudoseizures simulate the motor behavior of true seizures but do not involve abnormal electrical discharges. Pseudoseizures can be distinguished from true seizures by the form of the seizure and by the lack of the usual associated features. The form does not fit the known patterns for epileptic attacks and can consist of random flailing about. Furthermore, the form can be variable from seizure to seizure, lacking the stereotypy typical of true seizures. Incontinence and tongue biting are rare. There is minimal confusion at the conclusion of the episode, and no abnormalities are detected on neurological examination. EEG can be helpful in distinguishing pseudoseizures, especially if one can be obtained during an event and then studied for evidence of electrical discharges that would correspond with the motor behavior. An EEG obtained after a true seizure should demonstrate areas of slowing that would not be seen after a pseudoseizure. Serum prolactin levels increase markedly immediately after a

seizure and can be helpful in distinguishing true seizures from pseudoseizures. Video EEG telemetry is the definitive means of determining whether an observed seizure is epileptic in origin or a pseudoseizure.

Pseudoseizures are more likely in patients who suppress emotion or express emotion through somatic means. Pseudoseizures most often are conversion disorders in which the patient does not have conscious volitional control of the behavior; rarely are pseudoseizures the result of faking or malingering. Pseudoseizures frequently occur in patients who have true epileptic disorders, confounding the diagnosis. W. Alwyn Lishman has aptly noted that the diagnostic error of interpreting epilepsy as pseudoseizures is probably much more common than the reverse and is far more detrimental to the patient's well-being. The diagnosis of pseudoseizures rests not on the presence of any particular personality traits or identifiable psychosocial stressors, but rather on the form of the seizure, associated features, and EEG confirmation.

**Primary Psychiatric Disorders** The presence of intellectual deficits, whether identified with bedside procedures or on standardized neuropsychological tests, does not automatically warrant the diagnosis of a cognitive impairment disorder. Neuropsychological abnormalities occur frequently in many patient populations. Once neglected or considered epiphenomena of more central emotional disturbances, cognitive processing deficits are now known to be key components of clinical disorders such as major depressive disorder (especially in the elderly), acute and chronic schizophrenia, chronic alcohol dependence, and perhaps obsessive-compulsive disorder. Cognitive impairment disorders, such as dementia or delirium, or secondary psychiatric syndromes are all caused by specific disease processes; vigilant diagnostic evaluation usually leads to detection of a primary systemic or cerebral disturbance.

Difficulties may arise when the cause is presumed but cannot be proved, as in the case of dementia of the Alzheimer's type, where the definite diagnosis must await postmortem brain examination. When a patient has both a major depressive syndrome and clinical findings consistent with incipient dementia of the Alzheimer's type, it may not be possible to determine immediately the fundamental disturbance being evaluated. Such confusing situations typically arise with the near-simultaneous onset of both symptom clusters or in patients who have experienced major depressive disorder previously. Such patients require careful definition of symptoms, initiation of therapy for all potentially treatable conditions, and serial monitoring of the patient's responses. Documentation of the longer-term course also assists in disentangling and recognizing separately contributing disease processes.

Despite careful observation and follow-up evaluation, the clinician may remain uncertain whether a syndrome is idiopathic or secondary to other detected diseases. In such instances, it is preferable to diagnose a primary psychiatric condition on Axis I, define all systemic or cerebral conditions on Axis III, and thereafter maintain a high order of vigilance while monitoring the course of the disorder longitudinally. It is important to note questions or uncertainties in the medical record for later scrutiny, for that practice avoids premature diagnostic closure.

Clinicians must also guard against willingness to provide a psychiatric diagnosis when specialists from other medical disciplines have ruled out specific disease processes after laboratory tests have been

unrevealing. The failure to define an organic disease does not warrant a functional diagnosis by default. As emphasized in DSM-IV, specific clinical signs, symptoms, and course are needed to establish the presence of a primary psychiatric disorder.

**Metabolic Disorders** Because most systemic medical conditions can directly or indirectly affect brain function, any list of illnesses that may cause a secondary psychiatric syndrome or cognitive disorder must be incomplete. Table 10-17 lists some frequently described potential causes. The precise pathophysiological mechanisms by which the disease process alters brain function are poorly understood in most cases. More than one process may be involved. For example, a patient with acute myelogenous leukemia may have altered brain function resulting from the neoplastic process itself, anemia (with decreased oxygen delivery to the brain), brain hemorrhages (caused by thrombocytopenia), and infections.

**Table 10-17** Metabolic and Other Systemic Disturbances

Secondary psychiatric syndromes may be the first, most prominent, or only clinical phenomena to call attention to the underlying condition (e.g., depression due to occult pancreatic carcinoma and cognitive deficits due to vitamin $B_{12}$ deficiency even in the absence of other neurological or hematological signs). Secondary behavioral changes may also result from multiple etiologies, of which any one alone might or might not be sufficient to produce the psychiatric disturbance (e.g., delirium due to mild anemia, mild hyponatremia, and marginal hypoxemia). The rate of change may also be important with certain etiologies. For example, a sudden drop in serum sodium to 125 mEq/L is more likely to produce behavioral changes than a chronic hyponatremia of 125 mEq/L.

Etiologies particularly identified with specific psychiatric syndromes are discussed under each syndrome. However, most etiologies can produce more than one syndrome (e.g., hypothyroidism is most often associated with a depressive state but may also cause mania, delirium, or dementia). How a specific etiological factor causes varied behavioral changes presumably results from both trait-dependent and state-dependent brain diatheses that largely are not understood.

**Demyelinating Disorders** With regard to secondary psychiatric syndromes, multiple sclerosis is the most important demyelinating disorder. Although it may cause delirium, dementia, and nonaffective psychoses, mood disturbances have been described frequently. Isolated, persistent euphoria has long

been noted and is thought to be physiologically related to demyelinated lesions in the limbic system, frontal lobes, and basal ganglia (Fig. 10-8). *Emotional incontinence*, also termed *pathological laughing or weeping*, is a state of labile affective expression that is apparently disconnected from underlying mood. Although pathophysiological mechanisms remain uncertain, it is speculated that interruption of pathways between the telencephalon and lower regions is responsible.

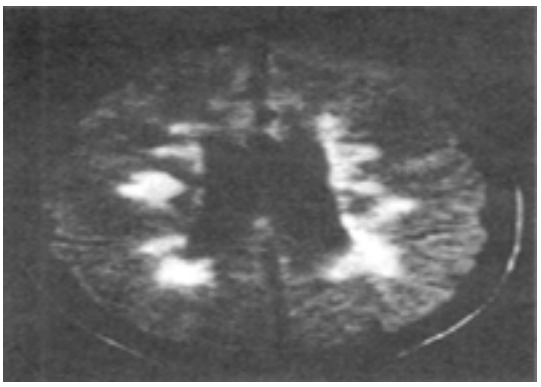


**FIGURE 10-8** MRI study of the head. Extensive confluent periventricular lesions are seen in a patient with multiple sclerosis. The corresponding CT scan was normal. (Reprinted with permission from Lukes SA, Crooks LE, Aminoff MJ, Kaufman L, Panitch HS, Mills C, Norman D: Nuclear magnetic resonance imaging in multiple sclerosis. Ann Neurol *13*:596, 1983.)

Depressive syndromes are especially prevalent in patients with multiple sclerosis. Most studies have focused on major depressive disorder or have not used specific diagnostic criteria; therefore, little is known about minor or other subsyndromal depressions. Some data suggest that depressive syndromes can be caused directly by the demyelinating process in specific CNS regions; for example, patients with cerebral disease have higher rates of depression than patients with spinal multiple sclerosis. However, there is also evidence implicating psychological and social factors in the pathogenesis of depression in these patients, and it is likely that many of their depressive syndromes are not secondary to or specifically symptomatic of cerebral disease.

Bipolar disorders are less well studied, although they appear to be more prevalent in multiple sclerosis populations than in the general population. Whether bipolar disorders in multiple sclerosis patients represent true secondary bipolar disorders, mania induced by treatments with corticosteroids, or manifestations of a shared genetic diathesis is not known.

Other demyelinating disorders include variants of acute encephalomyelitis (including postinfectious encephalomyelitis and acute posttraumatic demyelinization). These disorders generally manifest initially with coma or delirium, and survivors may have lasting cognitive and behavioral disturbances.

The treatment of psychiatric syndromes in demyelinating disorders, as for most secondary syndromes, is empirical and based on target symptoms (e.g., antipsychotic agents for psychosis). Studies suggest that antidepressant medications, when used in conjunction with supportive psychotherapy, are helpful in patients with multiple sclerosis. Tricyclic drugs, and possibly other classes of antidepressant drugs, reduce emotional incontinence associated with multiple sclerosis even in the absence of a full depressive syndrome.

**Degenerative Diseases** Degenerative disease processes involve deterioration of brain function resulting in the loss of previously attained capacities. Some degree of CNS degeneration occurs as part of the aging process and is reflected in alterations in gross brain structure; neuronal cell number, morphology, and function; and neurotransmitter synthesis, metabolism, and function. The degeneration manifests clinically with psychometrically definable cognitive declines, particularly in secondary or long-term memory, speed of mental processing, visuospatial processing, divided attention, and cognitive flexibility. A range of decrements is associated with normal aging, and clinicians and investigators are developing neuropsychological procedures that distinguish such normative processes from those associated with degenerative diseases. Indeed, DSM-IV includes age-related cognitive decline as a clinical condition that may be a focus for clinical attention although it is not a mental disorder. It allows physicians to explain to concerned healthy patients that their aging-associated decrements in cognitive processing are distinctive from incipient dementia. Other similar conditions include problems such as borderline mental functioning or bereavement.

However, the border between normative cognitive changes and incipient dementia is ill defined. Patients who present with acquired deficits below the normal range are at higher risk statistically of developing progressive problems. However, cross-sectional cognitive tests cannot reveal time of onset, and in some individuals test results are always below normal. Conversely, people with above-average intellectual abilities may experience cognitive decline without exhibiting objective deficits because their performance remains within normal limits despite obvious functional impairments. Degenerative CNS diseases can produce disturbances in cognition, mood, behavior, personality, and motor and perceptual function. In recent years investigators have more clearly defined that the major degenerative diseases (whether hereditary or idiopathic) reflect deterioration in specific or discrete neurochemical systems where there is as well a regional specificity that reflects the location of cell bodies and their ultimate terminal zones. Such diseases are best considered neurochemical system diseases and their general pattern is one of insidious onset with a gradual progression of deficits. Dementia is the most common syndromic presentation and worsens as a reflection of the long-term progressive process; it ultimately reflects widespread CNS disease. Secondary mood, psychotic, and personality syndromes are also seen but are more likely to manifest earlier in the course, when the degeneration may be more localized.

**Cortical and Subcortical Dementia** Degenerative CNS diseases can be distinguished clinically from one another by the relative impairment and sparing of various cognitive and behavioral functions. Two basic clinical patterns of dementia have been characterized clinically: *cortical* and *subcortical*. The cortical pattern of dementia is characterized by impairments in memory (primarily a storage and recall deficit) and gnostic-practic abilities (primarily involving language, visuospatial abilities, calculation, and motor praxis). Executive or managerial functions such as organization, judgment, abstraction, emotional control or modulation, and insight and social judgment are similarly affected. Fine and gross motor movements are generally preserved until later in the disease course. Personality often remains intact or displays subtle variations, with patients becoming more passive or less spontaneous, or becoming coarse and crude in their interactions. With disease progression the changes in personality become more common and pronounced. Affective expression is generally preserved, although again a coarsening may be noted in the form of emotional lability. Early in the disease, patients frequently discern and express

dismay about their intellectual decline.

The subcortical pattern is characterized by a generalized slowing of mental processing. Specific cognitive skills, such as calculation, naming, or copying are less affected initially, in contrast to their early decline in the cortical degenerative processes. Verbal and visual memory impairment may be present early in the course, although such impairment more often takes the form of forgetfulness or a failure of retrieval that is initially amenable to prompting, in contrast to the more severe recall deficits of cortical dementia. Patients also show deficits in learning new motor movements or complex psychomotor procedures. Planning and organizational skills are disrupted. Abnormal movements are common and manifest as a slowing and awkwardness in normal movement or as the intrusion of such extraneous movements as chorea or tremor. In contrast to the early impairment of language function in cortical disease, language is relatively spared, although the motor production of speech may be abnormal. The personality change is often marked, with striking patterns of apathy, inertia, and diminished spontaneity. Mood disorders, including major depression and mania, occur frequently. The presenting symptoms in subcortical degenerative processes may be those of a personality change or a mood disorder at a time when cognitive impairment or motor dysfunction is not yet obvious. In the cortical processes, by contrast, the presenting symptoms more often reflect cognitive impairment, particularly memory and language dysfunction. As the dementia and the degenerative process progress, the clinical presentations of cortical and subcortical diseases become nearly indistinguishable from one another.

The term “subcortical dementia” was first used to describe the cognitive and behavioral deficits seen in patients with Huntington's disease. A similar clinical pattern was soon described for other subcortical diseases, such as progressive supranuclear palsy and Parkinson's disease. Although the term was initially used in reference to a clinical picture that could be localized to the subcortex, *subcortical dementia* is now considered a pseudoanatomical designation. It is clear from imaging and neuropathological studies that cortical dementia (e.g., dementia of the Alzheimer's type) is not restricted pathologically to the cortex; major affected cholinergic fiber pathways are subcortical in origin. Subcortical diseases similarly affect regions outside the subcortex, especially the frontal lobes, because of the brain's robust frontal-subcortical connections. Moreover, failure of subcortical nuclei that directly receive cortical efferent pathways can lead to clinical symptoms whose cerebral level of origin cannot be differentiated. Nonetheless, the cortical-subcortical distinction has been of clinical utility in defining patterns of cognitive, behavioral, mood, personality, and motor impairment, especially in the early stages of the degenerative disease process.

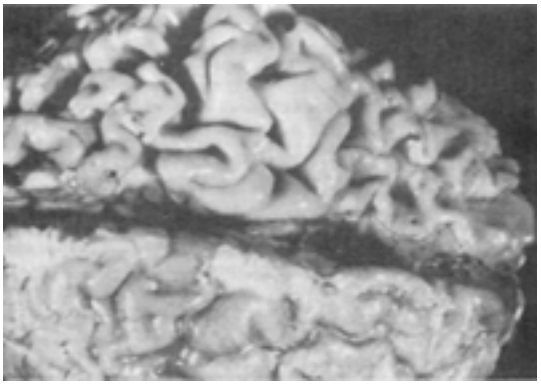
**Alzheimer's Disease** Alzheimer's disease is the prototype of a cortical degenerative disease. Alzheimer's original description in 1906 detailed most of the familiar clinical and neuropathological features. Of note, his patient suffered from paranoia in addition to cognitive decline. Currently, the diagnosis of Alzheimer's disease requires neuropathological confirmation, and the diagnosis is used clinically for cases identified antemortem. Age at onset is earlier in patients with a family history of the disease. Despite some data to suggest distinctive age-related clinical patterns, no phenomenological separation between early-onset and late-onset cases has been found consistently enough for age to substitute for detailed clinical description; however, early-onset dementia of the Alzheimer's type may have a more

rapidly progressive course. A major component of the presenting symptoms is usually subjective complaints of memory difficulty, language impairment (“I can't find the word”), and dyspraxia (e.g., difficulty driving). Diagnosis at this juncture is primarily based on exclusion of other possible etiologies for dementia. No features of the physical examination or laboratory evaluation are pathognomonic for dementia of the Alzheimer's type. Some studies have apparently discriminated patients with dementia of the Alzheimer's type from patients with dementia of other etiologies and from normal controls by using techniques such as EEG, MRI, and SPECT. These studies have been difficult to replicate consistently, and at present, brain-imaging studies are best used to exclude other identifiable causes. Indeed, available technological diagnostic methods have not proved more sensitive and specific than astute clinical evaluation in comparisons of patients with dementia of the Alzheimer's type and healthy control subjects. PET holds promise but currently is too expensive for clinical diagnostic use.

A variety of diagnostic criteria sets have been developed for dementia of the Alzheimer's type. Clinical criteria have been verified prospectively in autopsy studies and have been found to be highly specific although only moderately sensitive. Implementation of the criteria requires extensive evaluation, including an informant-based history, neurological examination, neuropsychological testing, and laboratory and neuroimaging data. Studies using clinical samples collected in research centers tend to show the highest correlation between premorbid diagnosis and postmortem histopathology. In part this reflects the sophisticatmon of the evaluators; also, research cohorts can exclude subjects who show signs of other confounding conditions during the evolving disease course. Recent studies have shown substantial inter-center diagnostic variation, as well as variation when using different diagnostic criteria. Variability is greatest in population studies, in contrast to clinical samples. Factors found to be protective in epidemiological studies include higher education, larger head circumference, and cigarette smoking. The latter factor likely reflects some type of neuroprotective effect of nicotine; the former two point to a “brain reserve” hypothesis, where the unknown deleterious effects of the basic Alzheimer's disease pathobiology are mitigated by initially having either more brain substance or greater associative connections because of the stimulator effects of education.

Alzheimer's disease is characterized pathologically by generalized atrophy of the cerebral cortex (Fig. 10-9) and by neurofibrillary tangles, neuritic (amyloid) plaques, and granulovacuolar degeneration (Fig. 10-10). Although plaques and tangles may be detected in the brains of the nondemented elderly, they are more numerous in patients with dementia. In recent years investigators have attempted to circumvent the qualitative overlap in symptoms by developing stricter quantitative, age-adjusted pathological criteria for Alzheimer's disease. Controversy remains whether brains with plaques from individuals without dementia were “normal variations” or early pathological signs of incipient disease. A definitive diagnosis ultimately requires both the characteristic dementia in life and the characteristic pathology after death.

**FIGURE 10-9** Alzheimer's disease. View of exposed left cortex showing severe atrophy. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*,



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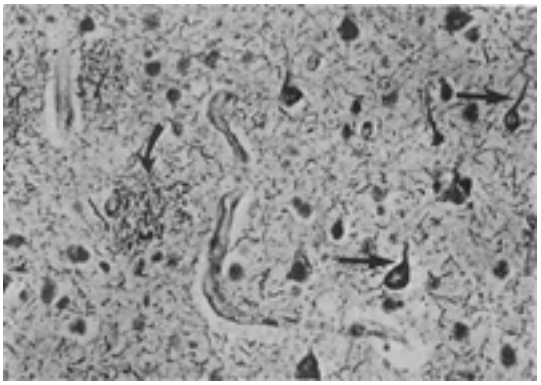


**FIGURE 10-10** Light micrograph of the cerebral cortex showing neurofibrillary tangles (arrows) and senile plaque (curved arrow) in Alzheimer's disease. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)

During recent years substantial effort has been devoted to the study of the molecular pathobiology of Alzheimer's disease, with the identification of at least four chromosomal loci associated with familial cases; the degeneration of central neurochemical systems, especially basal forebrain structures related to acetylcholine-mediated neurotransmission; factors associated with the formation of plaques and tangles; and exogenous (e.g., infectious and toxic) processes that may contribute to the development of sporadic cases. Molecular biologists have sought to understand the formation of the abnormal amounts of amyloid that constitute the cerebral plaques characteristic of the disease. Although amyloid itself is a normal brain product, it has been suggested that excessive amounts may be neurotoxic. Others continue to see amyloid accumulations solely as a disease byproduct. Attention has recently turned to amyloid precursor protein and the intriguing possibility of regulating amyloid production pharmacologically. The discovery of an association between apolipoprotein E4, controlled by a gene located on chromosome 19, suggests further avenues for investigating risk factors and pathogenetic mechanisms. Taken together, these recent findings point to a heterogeneous array of pathobiological processes contributing to the final clinical and histological picture known as Alzheimer's disease. The postmortem and antemortem presentations appear to be relatively generalized (i.e., nonspecific) outcomes of widely divergent etiologies.

The natural course of dementia of the Alzheimer's type, as of all the degenerative disorders, is exacerbation and progression of clinical symptomatology. Brain degeneration as measured by in vivo imaging techniques such as MRI has not been found to correlate closely with the state of clinical disease. The final common clinical picture is of a bedridden patient, wholly dependent on others for all basic functions, even for turning in bed. Nutrition can often be provided only by nasogastric or

gastrointestinal tubes. Death usually results from aspiration or from infectious processes associated with prolonged recumbency.

**Parkinson's Disease** Described by James Parkinson in 1817, Parkinson's disease is a prototype of a subcortical degenerative disease. It is idiopathic and must be distinguished from parkinsonian syndromes that arise from a variety of causes.

Parkinson's disease is the result of the degeneration of subcortical structures, primarily the substantia nigra but also the globus pallidus, putamen, and caudate (Fig. 10-11). Cells containing dopamine are predominantly affected, although serotonergic and other systems are disrupted as well. Just as the appellation “cortical pattern” is pseudoanatomical, so in subcortical Parkinson's disease there can be significant degeneration of cortical structures. The parkinsonian syndrome manifests with structural damage that reflects the underlying process or insult. Medication-induced parkinsonism presumably involves only a dysfunction of the basal ganglia structures, without any obvious pathoanatomical abnormality. The typical age at onset of Parkinson's disease is between 50 and 60 years but may vary widely, with onset sometimes occurring one to two decades earlier. The clinical course is chronic and progressive, with severe disability attained after approximately 10 years. A smaller proportion of patients have a more rapidly progressive disease, and a yet smaller group has a slowly progressive disorder in which deterioration plateaus or remains minimal for two to three decades.

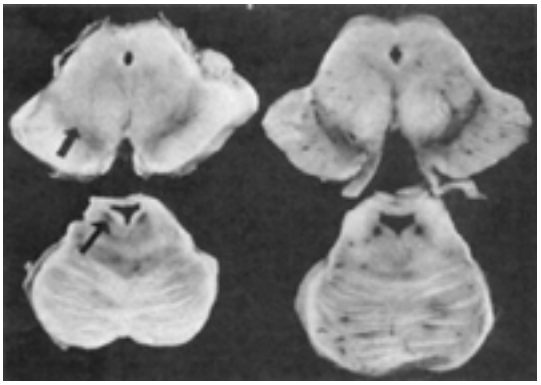


**FIGURE 10-11** Parkinson's disease. Section of midbrain and pons showing depigmentation of substantia nigra and locus ceruleus in Parkinson's disease on left (arrows) and normal substantia nigra and locus ceruleus on right. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)

In general, subcortical diseases are thought to impinge on the three Ms—movement, mentation, and mood. In Parkinson's disease all three of these areas are affected, although not always uniformly. The movement abnormalities are characterized by the triad of tremor, rigidity, and bradykinesia. The tremor and rigidity can be unilateral or bilateral. Bradykinesia is manifested by slowness in the initiation and execution of movement. The typical presentation, with a masklike facies, minimal blink, and monotonic speech, is a concomitant of the rigidity and slowness of movement. Other prominent characteristics include postural changes such as chin-to-chest flexion and gait abnormalities. The gait is characteristically slow and shuffling, and the patient has difficulty turning (en bloc turning) and trouble initiating and stopping walking. Seborrhea, sialorrhea, excessive fatigue, and constipation are also common.

Maurice Rosen was 69 when he made an appointment for a neurological evaluation. He had recently noticed that his memory was slipping and he had problems with concentration that were beginning to interfere with his work as a self-employed tax accountant. He complained of slowness and losing his train of thought. Recent changes in the tax laws were hard for him to learn, and his wife said he was becoming more withdrawn and reluctant to initiate activities. However, he was still able to take care of his personal finances and accompany his wife on visits to friends. Although mildly depressed about his disabilities, he denied other symptoms of depression, such as disturbed sleep or appetite, feelings of guilt, or suicidal ideation.

Mr. Rosen has a long history of treatment for episodes of depression, beginning in his 20s. He has taken a number of different antidepressants, and once had a course of electroconvulsive therapy. As recently as 6 months before this evaluation, he had been taking an antidepressant. Two years ago he developed an intermittent resting tremor in his left hand and a shuffling gait. Although the diagnosis of Parkinson's disease was considered by his psychiatrist, it was not confirmed by a neurologist, and therefore no additional treatment was given.

The neurologist who was now evaluating him found that his spontaneous speech was hesitant and unclear (dysarthric). Cranial nerve examination was normal. Motor tone was increased slightly in the neck and all limbs. Alternating movements of his hands were performed slowly. He had a slight intermittent tremor of the left arm at rest. Reflexes were symmetrical. A diagnosis of idiopathic Parkinson's disease was made, and he was placed on a low dose of carbidopa (Atamet), a medication that alleviates the symptoms of Parkinson's disease.

A neuropsychological examination performed 3 weeks later revealed average performance on the Wechsler Adult Intelligence Scale-Revised (full scale I.Q. = 104), but a verbal I.Q. of 118 and a performance I.Q. of 84. Memory as assessed by a 12-item, 10-trial, selective reminding task was poor, with no more than 7 items recalled on any trial, and only 3 words recalled after a 15-minute delay, although the patient could recognize the remaining words. He showed marked difficulty in drawings of overlapping figures and parallel lines. He was unable to draw three-dimensional figures. In language testing he demonstrated impaired naming. In summary, Mr. Rosen displayed evidence of impairment in memory, naming, and constructional abilities. These may have been secondary to slowness, poor planning, and perseveration. The deficits were believed to result from Parkinson's disease. Additional evaluation included an MRI, which revealed only generalized atrophy, and an EEG, which was significant for background generalized slowing. (Reprinted with permission from *DSM-IV Casebook*.)

Mentation or cognition in Parkinson's disease is an area of controversy. Most patients complain of slowed thinking, sometimes called bradyphrenia. In general, approximately 20 to 30 percent of patients with Parkinson's disease are found to have dementia, with the likelihood greater in those with late-onset disease (after age 70 years). Approximately 40 percent of nondemented patients with Parkinson's disease, however, demonstrate some neuropsychological impairment in most studies. The impairments are primarily in visuospatial capacities, as measured by copying, tracing, and tracking tasks, and in the

shifting of cognitive sets, as measured by the Wisconsin Card Sorting Test or the Stroop Test. Such deficits have been noted in the absence of cognitive-based functional decline or other evidence of cognitive impairment. Controversy has emerged over whether these two patterns represent a single continuum of dementia integral to the process of Parkinson's disease or are two separate processes indicative of two distinct diseases. Neuropathologically, cases intermediate between Parkinson's disease and Alzheimer's disease exist, with the characteristic microscopic features of the latter and Lewy bodies in the substantia nigra suggesting the former. There is no clear line of division as yet between a process resembling dementia of the Alzheimer's type on which abnormal parkinsonian movements are superimposed and a clinical presentation of Parkinson's disease in which the patient slowly develops a global progressive dementia.

Mood disorders have been frequently reported in association with Parkinson's disease. Depression is the most common; mania is virtually unreported. The mean frequency of depression is approximately 40 percent, with a reported range of 4 to 70 percent. No relation has been demonstrated between the frequency and severity of depression and the patient's current age, the age at onset of symptoms of Parkinson's disease, the duration of those symptoms, the severity of motor signs, or the response to medication. No relation has been demonstrated among mood, rigidity, bradykinesia, or tremor. Although depression has been found more commonly in patients with Parkinson's disease who display prominent gait and postural changes, the relation between mood and the severity of the disability is limited. There may be some association between depression and laterality of disease, for patients with left brain disease appear to have a higher frequency of depression than patients with right brain disease. This pattern suggests that the mood disturbance is a primary manifestation of brain deterioration and not a reactive psychological response to chronic illness and disability. Although the evidence relating lateralization to a higher frequency of depression is preliminary, it does recall data regarding poststroke depression and its putative relationship to left hemisphere localization but not to the extent of disability. The phenomenology of depression in Parkinson's disease is similar to that of idiopathic major depressive disorder, for it includes subjective dysphoria, pessimism, irritability, and suicidality, but perhaps less self-disparagement and self-blame. Some patients present with anxiety or panic attacks. Anergia, psychomotor retardation, and early-morning awakening are three symptoms that have been found to be nonspecific for depressive disorder in those patients, as they overlap considerably with the manifestations found in nondepressed patients with Parkinson's disease. Some data support the view that the depression of Parkinson's disease is associated specifically with decreased CNS serotonin concentrations. The on-off syndrome, in which patients experience severe fluctuations in mobility ranging from normal movement to a frozen state, has also been associated with changes in mood. On-off phenomena usually occur after years of chronic treatment with levodopa and can manifest as a between-dosage effect or randomly throughout the day. Many studies have reported changes in mood coincident with changes in motoric function, namely, subjective and objective dysphoria in the off period and, less frequently, abnormal elation and euphoria during the on period.

Psychosis as a concomitant of Parkinson's disease has been reported in the context of mood disorders (e. g., psychotic depression) or as a consequence of treatment. There are no reports of a specific personality change characteristic of Parkinson's disease except for the apparent apathy and lack of initiative that are often subsumed under bradykinesia and bradyphrenia.

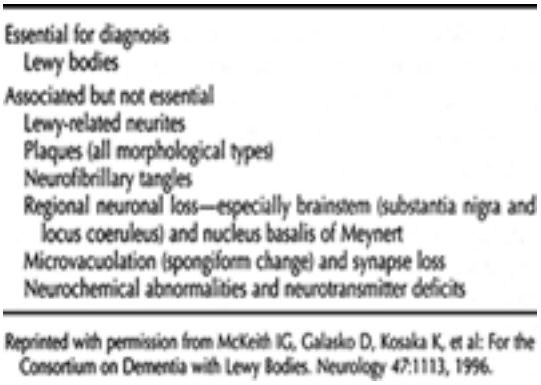
The pharmacological treatment of Parkinson's disease addresses mood and movement because there is no known regimen for the improvement of cognition. For movement dysfunction dopamine precursors, such as levodopa or levodopa-carbidopa, (Sinemet), are a mainstay of treatment. Gait, posture, rigidity, and akinesia are generally more responsive to levodopa than is tremor. Anticholinergic agents and the dopamine agonists (bromocriptine [Parlodel] and pergolide [Permax]) are second-line agents. The monoamine oxidase (MAO) type B inhibitor selegiline (Eldepryl) has been demonstrated to apparently slow the progression of motor dysfunction, although in the low doses used it did not have significant antidepressant efficacy. Its effects on the development of cognitive impairment are unknown. Currently a new generation of dopamine receptor agonists is emerging; their long-term utility will become clear in the coming years. All symptomatic antiparkinsonian agents can cause delirium, a common iatrogenic concomitant of the disease. Levodopa has also been reported to cause visual hallucinations in some patients, even in the absence of delirium. Surgical treatments—stereotactic lesioning of the thalamus or globus pallidus—were used in the past to alleviate the motor dysfunction of Parkinson's disease. Although that approach had largely been replaced by pharmacological treatment, newer and more precise operative procedures have been developed in the past few years. Transplantation of fetal neural tissue into the caudate of the adrenal medulla also has been attempted, but no data from well-controlled studies are available regarding the effects of the procedure on mood and mentation. Recent findings suggest that fetal tissue transplantation may dramatically alleviate severe motor symptoms. Many differences exist in surgical protocols and transplantation methods, underscoring the highly experimental nature of these procedures.

Treatment of the mood disorder associated with Parkinson's disease involves the same agents that have proved valuable in treating idiopathic major depressive order. Antidepressant medication from all categories have proved efficacious. ECT is of value for treating both the mood component and the motor dysfunction; dramatic improvement in all aspects of movement has been demonstrated on standardized neurological examinations. Several studies have reported sustained improvement in motor function for as long as 6 months after treatment; however, most detected a short-lived improvement of days to weeks. ECT is recommended for patients with Parkinson's disease and the on-off syndrome, particularly when significant mood changes are present.

In summary, Parkinson's disease is a prototypical subcortical pattern degenerative disease. The overlap of clinical phenomena between a basal ganglia disease, such as Parkinson's disease, and major depressive disorder can be striking. Both are characterized by qualitatively similar impairments in the realms of movement, mentation, and mood. Differing terminologies have arisen to describe similar signs and symptoms in each. *Psychomotor slowing (psychomotor retardation)* a term used to encompass both the motoric and cognitive slowing seen in depression, is quite similar to the bradykinesia and bradyphrenia described early in the course of Parkinson's disease. A recent study that used a nonmotor measure of bradyphrenia demonstrated close correlations between cognitive slowing and severity of the mood disorder both in depressed patients with Parkinson's disease and patients with idiopathic major depressive disorder, suggesting a close phenomenological relation between the bradyphrenia of Parkinson's disease and so-called psychomotor slowing. It underscored the idea that basal ganglia disorders are fertile ground for research and insight into the neurobiological bases of idiopathic mood

disorders.

**Dementia With Lewy Bodies** Since the late 1980s research has revealed that, beyond dementia of the Alzheimer's type and vascular dementia, a common cause of progressive dementia may be related to the presence of Lewy bodies in the brainstem and cerebral cortex. Lewy bodies—intracytoplasmic, spherical, eosinophilic neuronal inclusion bodies—are scattered through the brainstem, subcortical nuclei, limbic cortex (cingulate, entorhinal, amygdala), and neocortex (temporal > frontal = parietal). Parkinson's disease, in contrast, manifests Lewy bodies in subcortical nuclei, in addition to degeneration of dopamine cell bodies in substantia nigra. Table 10-18 lists the pathological features of dementia with Lewy bodies; Table 10-19 includes recently developed consensus guidelines for clinical diagnosis. Neuropsychiatric features, including visual hallucinations, delusions, fluctuating attention, and executive or managerial cognitive deficits, are prominent; although not specific, mood disturbances are common.



Essential for diagnosis
- Lewy bodies

Associated but not essential
- Lewy-related neurites
- Plaques (all morphological types)
- Neurofibrillary tangles
- Regional neuronal loss—especially brainstem (substantia nigra and locus coeruleus) and nucleus basalis of Meynert
- Microvacuolation (spongiform change) and synapse loss
- Neurochemical abnormalities and neurotransmitter deficits

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**Table 10-18** Pathological Features Associated With Dementia With Lewy Bodies

1. The central feature required for a diagnosis of dementia with Lewy bodies is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for a diagnosis of probable dementia with Lewy bodies, and one is essential for possible dementia with Lewy bodies:
   a. Fluctuating cognition with profound variations in attention and alertness
   b. Recurrent visual hallucinations that are typically well formed and detailed
   c. Spontaneous motor features of parkinsonism
3. Features supportive of the diagnosis are:
   a. Repeated falls
   b. Syncope
   c. Transient loss of consciousness
   d. Neuroleptic sensitivity
   e. Systematized delusions
   f. Hallucinations in other modalities
4. A diagnosis of dementia with Lewy bodies is less likely in the presence of:
   a. Stroke disease, evident as focal neurologic signs or on brain imaging
   b. Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

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**Table 10-19** Consensus Criteria for the Clinical Diagnosis of Probable and Possible Dementia With Lewy Bodies

**Substance-Induced Disorders** Pharmacological compounds are potent and frequent causes of psychopathology. This effect, especially when caused by environmental and occupational neurotoxins, has been little studied; more attention has been paid to peripheral or motor effects than to the less easily quantified behavioral alterations. Although alcohol-induced neuropsychiatric syndromes have long been known of, the CNS consequences of abuse of recreational drugs received attention only in recent decades, in part because of societal disapproval of recreational drug use, disinterest among investigators, and the inherent difficulty of separating drug effects from confounding person effects.

Broadly speaking, there are four classes of chemically induced psychopathology: (1) that due to environmental contamination, both natural (e.g., venoms and poisonous foods) and human-made (e.g., gasoline contamination of well water); (2) that due to occupational exposure; (3) that due to recreational use, abuse, or dependence on substances causing transient or lasting CNS toxic effects; and (4) the iatrogenic complications of prescribed or over-the-counter medications. Compounds must be considered from the perspectives of (1) acute or immediate effects (e.g., behavioral symptoms of acute intoxication), (2) longer-term responses to persistent exposure, and (3) lasting consequences that persist after the cessation of any direct pharmacological action. The last may be especially complex because of the extremely prolonged retention (months to years) of some compounds within the body.

When considering the possibility of drug- or toxin-induced psychopathology, the clinician must undertake a careful chain of reasoning, akin to deciding on any secondary diagnosis but differing in several respects. Initially, the clinician must ascertain whether an exposure occurred and at what level; for example, an industrial hygienist may have been exposed in a possible occupational incident. Next, it is critical to understand the toxicity of a substance (especially as it might relate to different chemical forms), its mode of action (when known), its effects in various animal species, and its clinical manifestations. Typically, these issues are within the realm of toxicologists. Subsequently, the clinician seeks to define the systemic clinical manifestations of the exposure in the particular patient. Although behavioral changes may be the only exposure-related findings, more often there is a variety of consistent symptoms, signs, and laboratory findings that together make a coherent clinical picture. It is within that larger context that the clinician views any presumptively related psychopathology.

When attempting to establish a neurotoxic diagnosis, physicians also must recognize other cardinal features of toxic exposures that influence clinical reasoning: (1) neurotoxic chemicals often cause nonfocal/nonspecific syndromes; (2) standard laboratory tests may have limited diagnostic utility; (3) there usually are strong dose-response relationships; (4) a single toxin may produce multiple syndromes; (5) with a few specific exceptions (e.g., asbestos, therapeutic cerebral radiation exposure), toxin-induced illnesses occur concurrently with exposure or following a short latency period; (6) the chemical formula may not predict toxicity; (7) a compound without known neurotoxic activity can interact or potentiate the effects of known neurotoxins; and (8) neurotoxic disease often may be asymptomatic.

Ideally, one would like to know the neuropsychiatric effects of all CNS toxic compounds. In the absence of such information, the clinician must describe symptoms and signs in detail and compare them with available data. The clinician defines the temporal course of exposure and assesses how the emergence of specific psychiatric manifestations relates to known actions of the compounds in question. Simultaneously, the clinician must consider the form of the disorder and establish whether it suggests a pathological CNS process or is more consistent with primary (idiopathic) psychopathology. The clinician must decide whether the syndrome in question might reflect other unrelated disease processes as well. Any measurable clinical and laboratory manifestations of CNS disease should be identified. Although no single measurement can be considered proof, taken together such measurements offer the possibility of establishing a diagnosis with a high degree of clinical certainty.

The array of environmental and occupational compounds to which people may be exposed is large.

Except for patients exposed to recreational and iatrogenic agents, until recently most psychiatrists did not treat patients with toxic exposures. This is changing rapidly as a result of late twentieth-century technology and increasing societal awareness. The clinician should remember that toxic exposures are used by some patients to explain a pantheon of personal ills, many of a psychiatric nature. It is neither appropriate to treat those complaints lightly nor clinically sound to accept such pathogenic explanations without firm clinical support.

Recreational drugs may be used or abused intentionally to cause dose-dependent behavioral changes, including anxiolysis with nicotine, intoxication with alcohol or marijuana, or psychosis with mescaline. There may be additional unwanted psychiatric phenomena with drug intoxication. Unwanted secondary syndromes commonly described include anxiety and insomnia due to caffeine; paranoid psychosis with cocaine; mood alterations (dysphoria, anxiety, euphoria) accompanying the perceptual disturbances induced by hallucinogenic substances; agitated (often violent) psychotic states with phencyclidine (PCP); and depressive symptoms and seemingly paradoxical disinhibition of aggressive impulses with sedative-hypnotic agents. However, there may be considerable variability and therefore lack of specificity in syndromic association with particular substances. Also, many substances in sufficient doses can cause delirium, which may itself have associated psychiatric symptoms ranging from mood disturbance to psychosis.

Withdrawal syndromes are also commonly encountered with drugs of abuse and tend to be characteristic of the class of drug. Withdrawal from nicotine may produce anxiety or irritability; withdrawal from stimulants produces a hypersomnic dysphoric crash; and withdrawal from opiates produces a well-described state that includes malaise, anxiety and irritability, drug craving, insomnia, psychomotor agitation, anorexia, and a variety of physical symptoms (e.g., diarrhea, piloerection, mydriasis, hypertension, and tachycardia). Delirium often follows withdrawal from alcohol and sedative-hypnotic medications but is not a component of other drug withdrawal syndromes (e.g., opioid-related).

Numerous medications have been implicated in causing psychiatric phenomena. Prescription drugs and over-the-counter preparations may cause physiologically induced behavioral changes, either through intoxication (which may involve use at therapeutic or supratherapeutic levels) or withdrawal. As with other causes of secondary psychiatric disorders, combinations of medications and medical illnesses may cause behavioral changes even when each medication or illness alone does not.

Among prescribed medications, psychotropic drugs are designed to effect behavioral changes. Unwanted psychiatric syndromes, such as antipsychotic-induced depressive syndromes or the delirium of lithium toxicity, occur often. Countless medications have been implicated in secondary psychiatric syndromes; it is rare indeed for a medication to be listed in the *Physicians' Desk Reference* without an accompanying description of some potential neuropsychiatric adverse effect. However, this information must be interpreted with caution. Behavioral adverse effects are also noted with placebos; therefore, distinguishing physiological from psychological symptoms may be difficult. Psychiatric symptoms may also reflect the clinical manifestations of the primary illness being treated (e.g., delirium in a patient receiving a new parenteral antibiotic may be due to the antibiotic or the targeted infection). Finally, numerous other factors may complicate the process of establishing the etiological significance of a

particular medication. For example, β-adrenergic-receptor antagonists have been postulated for many years to cause depressive syndromes, yet a recent large study, carefully controlled for patient demographics, medical illness, medications, and other factors, was unable to find a significant independent association between β-adrenergic receptor antagonists and depression. Despite these caveats, many medications clearly can cause secondary psychiatric syndromes.

## COGNITIVE DISORDERS

**Delirium** Delirium, a transient disorder of brain function manifested by global cognitive impairment and other behavioral phenomena, is a common disease state that has been described for centuries. Nevertheless, it is frequently missed or misdiagnosed, with the potential for substantial attendant morbidity and mortality. Recognition and appropriate evaluation and treatment of delirium should be an imperative, not just for psychiatrists but for all physicians.

**Definition** DSM-IV includes delirium under cognitive disorders. Delirium is a syndrome, with core features of impairment of consciousness with attentional deficit, other cognitive alterations, and a relatively rapid onset of the disorder with a characteristically fluctuating course. Frequently there are other associated clinical phenomena, which may appear more prominent to the uneducated observer than the core features.

### History

Physicians have long recognized states of altered behavior, including changes in level of consciousness, of acute onset that were associated with fever, poisons, or other medical or neurological diseases. There are references to such presentations in the writings of Hippocrates and in much subsequent Greco-Roman literature. Descriptions of the syndrome similar to modern definitions appear from the late Middle Ages through the eighteenth century. The history, however, is obscured by an etymological web that to this day impedes communication and education about the disorder. Numerous terms have been used to describe the syndrome of delirium, including *phrenitis, frenzy*, and *febrile insanity*; conversely, the term “delirium” has also been applied to other psychiatric states that led to insanity.

By the nineteenth century emphasis was placed on disordered consciousness as the hallmark of delirium. The phrase “clouding of consciousness” dates to that time and is still used in many quarters today despite lack of clarity as to what it means. Similarly, the term “confusion” was used frequently, despite the lack of a specific relation to delirium.

The work of George Engel and John Romano in the 1940s, summarized by them in publications from the 1950s, indicated that attentional and other cognitive disturbances were best viewed as the core features of the syndrome and that the state was associated with acute brain failure, as demonstrated by slowing on the EEG. Subsequent work on the pathophysiology of delirium has been relatively scant. Zbigniew Jerzy Lipowski, beginning in the 1960s and continuing to the present, has been instrumental in raising clinical and research awareness of delirium, defining the syndrome according to strict criteria and

popularizing (especially in the psychiatric community) the use of the term “delirium.” Recent years have seen alterations in diagnostic criteria, as evidenced by the removal of associated clinical features such as psychomotor changes from the required criteria. There has also been increasing study of epidemiology, clinical course, and risk factors for onset or poor outcome.

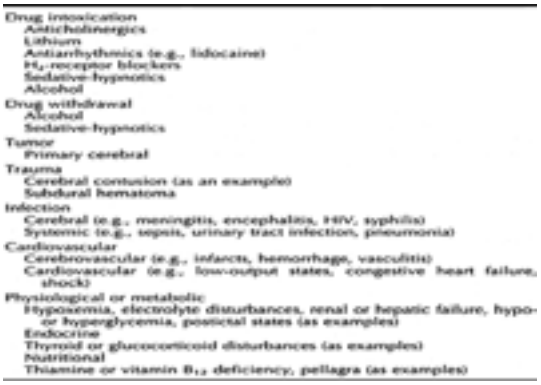
Unfortunately, etymological confusion remains. Numerous synonyms remain in common use, especially in nonpsychiatric medical fields; some of them are encephalopathy, acute confusional state, and acute organic brain syndrome. Some neurologists maintain a distinction between delirium, which they reserve to describe extremely agitated delirious states with frank thought process disorganization, perceptual disturbances, and autonomic hyperactivity, and acute confusional states, which they use to describe all other, often less severe delirious states. Most psychiatrists, and many other workers in the field, believe that such distinctions are premature at best (because of a lack of evidence of differing causes or pathophysiologies between the two) and misleading at worst, obscuring the commonality of core clinical features, potential etiologies, and management approaches.

**Epidemiology** There have been relatively few studies of the incidence and prevalence of delirium. Little is known about the epidemiology of delirium in community or other nonpatient, noninstitutionalized populations. An estimated 10 to 15 percent of general medical inpatients are delirious at any given time, and studies indicate that as many as 30 to 50 percent of acutely ill geriatric patients become delirious at some point during their hospital stay. Rates of delirium in psychiatric and nursing home populations are not well established but are clearly substantial. Risk factors for the development of delirium include increased severity of physical illness, older age, and baseline cognitive impairment (e.g., due to dementia).

Delirium is frequently unrecognized by treating physicians. Because of its wide array of associated symptoms, it may be detected but misdiagnosed as depression, schizophrenia, or other psychiatric disorder. Delirium is a frequent cause for psychiatric consultation in the general hospital but often is not recognized as such by the referring physician.

**Etiology** The syndrome of delirium reflects brain dysfunction that is almost always due to identifiable systemic or cerebral disease or to drug intoxication or withdrawal. A partial list of frequently encountered causes is given in Table 10-20. Often delirium is due to multiple simultaneous causes, each one of which may or may not be enough to cause delirium by itself. On rare occasions a syndrome nearly indistinguishable from delirium may manifest as part of the course of another Axis I disorder such as bipolar I disorder.

**Table 10-20** Causes of Delirium



Drug intoxication
- Anticholinergics
- Lithium
- Antiarrhythmics (e.g., lidocaine)
- $H_2$-receptor blockers
- Sedative-hypnotics
- Alcohol

Drug withdrawal
- Alcohol
- Sedative-hypnotics

Tumor
- Primary cerebral

Trauma
- Cerebral contusion (as an example)
- Subdural hematoma

Infection
- Cerebral (e.g., meningitis, encephalitis, HIV, syphilis)
- Systemic (e.g., sepsis, urinary tract infection, pneumonia)

Cardiovascular
- Cerebrovascular (e.g., infarcts, hemorrhage, vasculitis)
- Cardiovascular (e.g., low-output states, congestive heart failure, shock)

Physiological or metabolic
- Hypoxemia, electrolyte disturbances, renal or hepatic failure, hypo- or hyperglycemia, postictal states (as examples)

Endocrine
- Thyroid or glucocorticoid disturbances (as examples)

Nutritional
- Thiamine or vitamin $B_{12}$ deficiency, pellagra (as examples)

**Diagnosis and Clinical Features** The syndrome of delirium is almost always caused by one or more systemic or cerebral derangements that affect brain function.

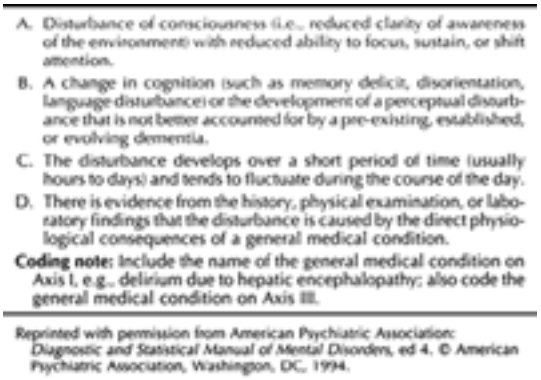
A 74-year-old African-American woman, Ms. Richardson, was brought to a city hospital emergency room by the police. She is unkempt, dirty, and foul smelling. She does not look at the interviewer and is apparently confused and unresponsive to most of his questions. She knows her name and address, but not the day or the month. She is unable to describe the events that led to her admission.

The police reported that they were called by neighbors because Ms. Richardson had been wandering around the neighborhood and not taking care of herself. The medical center mobile crisis unit went to her house twice, but could not get in and presumed she was not home. Finally, the police came and broke into the apartment, where they were met by a snarling German shepherd. They shot the dog with a tranquilizing gun, and then found Ms. Richardson hiding in the corner, wearing nothing but a bra. The apartment was filthy, the floor was littered with dog feces. The police found a gun, which they took into custody.

The following day, while Ms. Richardson was awaiting transfer to a medical unit for treatment of her out-of-control diabetes, the supervising psychiatrist attempted to interview her. Her facial expression was still mostly unresponsive, and she still didn't know the month and couldn't say what hospital she was in. She reported that the neighbors had called the police because she was “sick,” and indeed she had felt sick and weak, with pains in her shoulder; in addition, she had not eaten for 3 days. She remembered that the police had shot her dog with a tranquilizer, and said the dog was not in “the shop” and would be returned to her when she got home. She refused to give the name of a neighbor who was a friend, saying, “he's got enough troubles of his own.” She denied ever being in a psychiatric hospital or hearing voices, but acknowledged that she had at one point seen a psychiatrist “near Lincoln Center” because she couldn't sleep. He had prescribed medication that was too strong, so she didn't take it. She didn't remember the name, so the interviewer asked if it was Thorazine. She said no, it was “allal.” “Haldol?” asked the interviewer. She nodded. The interviewer was convinced that was the drug, but other observers thought she might have said yes to anything that sounded remotely like it, such as “Elavil.” When asked about the gun, she denied, with some annoyance, that it was real and said it was a toy gun that had been brought to the house by her brother, who had died 8 years ago. She was still feeling weak and

sick, complained of pains in her shoulder, and apparently had trouble swallowing. She did manage to smile as the team left her bedside. (Reprinted with permission from *DSM-IV Casebook*.)

DSM-IV gives separate diagnostic criteria for delirium due to a general medical condition (Table 10-21), for delirium related to systemic medical conditions or primary cerebral conditions, substance intoxication delirium (Table 10-22), substance withdrawal delirium (Table 10-23), delirium due to multiple etiologies (Table 10-24), and delirium not otherwise specified (Table 10-25) for a delirium of unknown cause or due to causes not listed, such as sensory deprivation. However, the core syndrome is the same, regardless of cause.



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

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

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

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

**Coding note:** Include the name of the general medical condition on Axis I, e.g., delirium due to hepatic encephalopathy; also code the general medical condition on Axis III.

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**Table 10-21** DSM-IV Diagnostic Criteria for Delirium Due to a General Medical Condition

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

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

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

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

**Note:** This diagnosis should be made instead of a diagnosis of substance intoxication only when the cognitive symptoms are in excess of those usually associated with the intoxication syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

**Note:** The diagnosis should be recorded as substance-induced delirium if related to medication use.

*Code:* [Specific substance] intoxication delirium (Alcohol; amphetamine (or amphetamine-like substance); cannabis; cocaine; hallucinogen; inhalant; opioid; phencyclidine (or phencyclidine-like substance); sedative, hypnotic, or anxiolytic; other (or unknown) substance (e.g., cimetidine, digitalis, benztropine))

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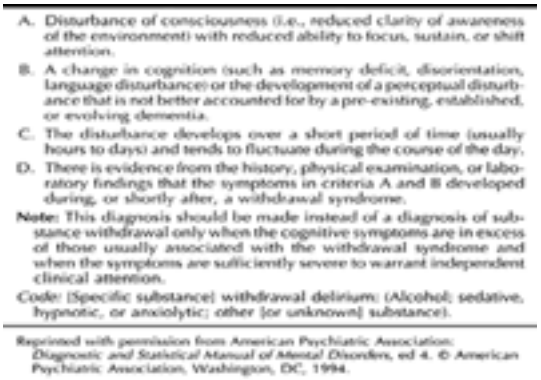
**Table 10-22** DSM-IV Diagnostic Criteria for Substance Intoxication Delirium



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

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

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

D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.

**Note:** This diagnosis should be made instead of a diagnosis of substance withdrawal only when the cognitive symptoms are in excess of those usually associated with the withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

*Code:* [Specific substance] withdrawal delirium: (Alcohol; sedative, hypnotic, or anxiolytic; other (or unknown) substance).

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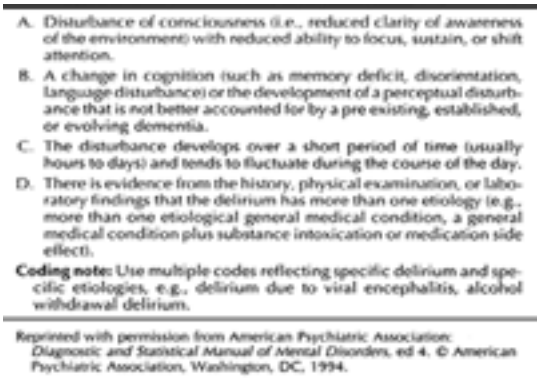
**Table 10-23** DSM-IV Diagnostic Criteria for Substance Withdrawal Delirium



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

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

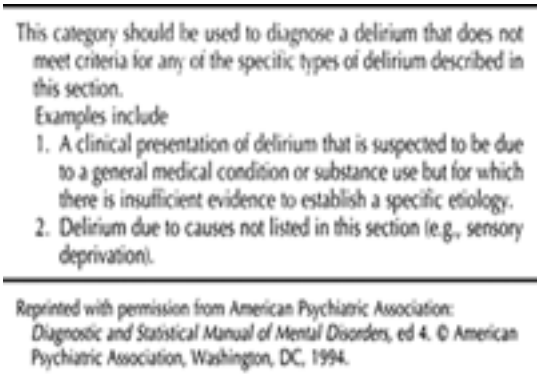
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination, or laboratory findings that the delirium has more than one etiology (e.g., more than one etiological general medical condition, a general medical condition plus substance intoxication or medication side effect).

**Coding note:** Use multiple codes reflecting specific delirium and specific etiologies, e.g., delirium due to viral encephalitis, alcohol withdrawal delirium.



**Table 10-24** DSM-IV Diagnostic Criteria for Delirium Due to Multiple Etiologies



This category should be used to diagnose a delirium that does not meet criteria for any of the specific types of delirium described in this section.

Examples include

1. A clinical presentation of delirium that is suspected to be due to a general medical condition or substance use but for which there is insufficient evidence to establish a specific etiology.
2. Delirium due to causes not listed in this section (e.g., sensory deprivation).



**Table 10-25** DSM-IV Diagnostic Criteria for Delirium Not Otherwise Specified

The core features of delirium include altered consciousness, such as decreased level of consciousness; altered attention, which may include diminished ability to focus, sustain, or shift attention; impairment in other realms of cognitive function, which may 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 quite severe cognitive impairment and disorganization.

Associated clinical features are often present and may be prominent. They may 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 due to alcohol or sedative-hypnotic withdrawal have low-voltage fast activity.

ICD-10 takes a somewhat different approach to establishing the diagnosis of delirium (Table 10-26). It requires the concurrent presence of disturbances in consciousness and attention, perception, thinking, psychomotor behavior, emotion, and the sleep-wake cycle. All features must be present to some degree for a definite diagnosis, thus making for a more restrictive classification than DSM-IV. The key to

diagnosing delirium is to maintain a heightened suspicion for the syndrome whenever a patient experiences a relatively rapid change in or the new onset of any psychiatric symptom or sign. Once the diagnosis is suspected, the history (usually obtained from informants such as family, nursing staff, and prior treaters) and mental status examination can elucidate the cognitive disturbances at the core of the syndrome and uncover associated clinical phenomena that may affect management or suggest the etiology.

**Table 10-26** ICD-10 Diagnostic Criteria for Delirium, Not Induced by Alcohol and Other Psychoactive Substances

The presence of delirium should prompt careful investigation for contributing causes. Delirium may be the first, most prominent, or only clinical manifestation of the new onset of a medical condition or the worsening of a previously diagnosed illness. A careful medical history (including medication and drug history), physical examination, and neurological examination must be undertaken, and various laboratory tests, neuroimaging procedures, lumbar puncture, and EEG may be useful. In searching for cause, physicians should remember that relatively minor abnormalities (e.g., a mild anemia plus slight hyponatremia plus slight hypercalcemia) may additively produce delirium even if each abnormality alone would not normally do so. Sometimes the search for an etiology does not yield a clear cause of the delirium; the patient still has the syndrome of delirium, however, and vigilance for clinical contributing factors must be maintained. Physicians should avoid the common mistake of believing delirium to be ruled out by the lack of obvious etiology, thereby proving that the behavioral disturbance is functional in origin. EEG may be helpful in such cases by demonstrating diffuse brain dysfunction, although that in itself does not demonstrate etiology.

Current understanding of the pathophysiology of delirium is limited. Dysfunction of the reticular activating system has been speculated, given its role in arousal. There is evidence for hypofunction of cholinergic systems, particularly in the basal forebrain and pons. There is some evidence for dysfunction of several other neurochemical systems, including noradrenergic, GABAergic, and serotonergic; more undoubtedly await investigation. Earlier speculation about globally decreased cerebral metabolism has not been confirmed, but also has not been carefully studied in delirium despite the availability of techniques such as PET and SPECT. Even more obscure is the pathophysiological link between specific systemic conditions and delirium. The classic model of such a link is anticholinergic drug toxicity, which has been presumed to cause delirium as a direct consequence of hypoactivity of cholinergic systems. Some recent work has demonstrated increased GABAergic transmission, putatively because of increased concentrations of endogenous benzodiazepine-like substances, in patients with delirium and

fulminant liver failure.

**Differential Diagnosis** Much attention has been given to differentiating delirium from dementia. Usually that distinction can be easily made by noting temporal factors (course of onset and progression of the disturbance) and by recognizing that level of consciousness and attention are affected prominently and early in delirium. Dementia by definition does not involve an alteration of consciousness, although attentional dysfunction develops as the syndrome progresses in severity. However, delirium is often superimposed on a pre-existing dementia. If the history is unknown and mental status examination results are lacking in a patient with severe dementia, it can be difficult to tell if there is a new delirium, or if the delirium has resolved and the patient is back to baseline (which may be a new baseline reflecting deterioration from a previous level of function). In such cases it is prudent to assume that the patient has delirium and to proceed with a careful clinical evaluation.

Although thought process disorganization, perceptual disturbances, or mood symptoms may lead the uninitiated to diagnose idiopathic psychiatric illness, the constellation of altered level of consciousness, prominent attentional and other cognitive deficits, and temporal course usually makes the differentiation of delirium from mood, psychotic, and anxiety disorders straightforward. The previous psychiatric history can be helpful, but the clinician must use care in interpreting it because patients with chronic psychiatric illness are also at risk for developing delirium due to medications, drug abuse, or other conditions. Rarely, patients with other Axis I illnesses (particularly the schizophrenias and bipolar disorders) may develop flagrantly disorganized, incoherent states with obvious attentional impairment and the examiner may be unable to test their other cognitive functions. (When found in the course of bipolar disorder, this state has been incorrectly called manic delirium.) Such states cannot be reliably distinguished phenomenologically from delirium due to the more usual medical causes, and they warrant the same thorough search for contributing etiologies accorded other deliria.

**Course and Prognosis** By most definitions, although not by DSM-IV criteria, delirium is a transient condition. For most patients the syndrome resolves within days to a few weeks. However, in sicker populations the mortality associated with delirium is high in the short term (acute hospitalization) and increases with several months of follow-up. It is not clear if increased mortality is independently associated with delirium or if it can be accounted for by known medical pathology. In some patients an apparently new dementia becomes evident on resolution of the delirium; the dementia may not have been present or may have been present but unrecognized prior to the delirium.

**Treatment** The primary treatment of delirium is to identify and ameliorate any causal or contributing medical conditions. As part of that effort, the dosages of all sedatives and other CNS-active medications should be minimized as much as possible. (The exception is sedative-hypnotic or alcohol withdrawal delirium, in which treatment of the underlying problem requires the administration of a cross-tolerant agent such as a benzodiazepine.) Delirious patients may need extra supportive physical care; maintenance of basic functions such as food and fluid intake is crucial to rapid recovery. Keeping the patient in an environment that is quiet and free of unnecessary stimulation may help reduce agitation. Frequent cues to orientation may also be helpful. Supportive contacts with the patient, family, and sometimes staff members are necessary to reassure the patient that the new, often frightening behavioral

state reflects physical illness and that the patient is not going crazy. Attention may need to be paid to the patient's legal capacity to participate in informed clinical care decisions.

The patient with a quiet, hypoactive delirium needs no specific pharmacotherapy. However, many delirious patients show persistent or intermittent psychomotor agitation that may interfere with nursing care or necessary tests and procedures. Control of the agitation is essential to prevent inadvertent self-damage and allow appropriate evaluation and treatment. Physical restraints may be used transiently when necessary. If sedation is desired, the drug of choice is a high-potency antipsychotic agent in relatively low dosages (e.g., haloperidol 0.5 to 1 mg orally or parenterally, up to several mg a day). Low-potency agents, benzodiazepines, and other sedatives (antihistamines, barbiturates) should generally be avoided because they are likely to worsen the delirious state. At times of severe, life-threatening agitation (e.g., if a patient in the intensive care unit is removing the endotracheal tube, arterial lines, and so forth), sedation at nearly any cost becomes necessary, and combinations of antipsychotic agents, benzodiazepines, and opioids have been used, as have neuromuscular-blocking agents, such as pancuronium (Pavulon), use of which depends on the availability of adequate ventilatory support).

There have been case reports of improvement in or remission of delirious states due to intractable medical illnesses with ECT. Although ECT may rarely be advised by a consultant with expertise in the procedure, routine consideration of ECT for delirium is not advised.

**Dementia** Interest in the study and care of patients with dementia has increased, coincident with the proportional increase of the elderly in the population. Although dementing disorders are defined by their multiple cognitive deficits, patients can present with the full array of psychiatric symptoms. And although dementia is most often associated with progressive processes, it does not by itself denote a deteriorating course. Thus, the clinician must seek any curable or treatable causes of dementia whenever it is recognized clinically, before irreversible CNS changes supervene.

**Definition** Dementia is a diminution in cognition in the setting of a stable level of consciousness. Dementia denotes a decrement of two or more intellectual functions, in contrast to focal or specific impairments such as amnestic disorder or aphasia. The persistent and stable nature of the impairment distinguishes dementia from the altered consciousness and fluctuating deficits of delirium. Dementia must also be distinguished from long-standing mental subnormality, as the former represents an acquired loss of or decline in prior intellectual and functional capacities.

## History

*Dementia* has long been understood as describing an acquired cognitive and behavioral decline associated with brain disease. Jean Étienne Dominique Esquirol, in his classic, early nineteenth-century nosological work, *Mental Maladies: A Treatise on Insanity*, provided perhaps the first modern definition of dementia: “A cerebral affection usually chronic . . . and characterized by a weakening of the sensibility, understanding, and will.” In his study of over 300 patients, Esquirol described the noncognitive symptoms of dementia, reporting hallucinations, delusions, aggressive behavior, and motor

abnormalities in many of the patients. Interestingly, however, he included among the causes of dementia not only aging, head trauma, syphilis, and alcohol abuse, but also conditions such as “menstrual disorders, . . . onanism, . . . disappointed affections, . . . and political shocks.” Later investigators described neuropathological correlations for the dementia syndromes, firmly establishing the relation between brain disease and dementia. Contemporary interest has focused again on an etiological basis for the observed pathological and pathophysiological abnormalities and on risk factors, preventive measures, and specific treatments for dementia.

**Comparative Nosology** In DSM-III and DSM-III-R, dementia was listed as both a syndrome and a disorder. The development of specific criteria for the symptom constellation was a major departure from all previous nosologies. It proved to be a major conceptual advance for clinical practice and research. The dementia syndrome was one of the possible presentations of psychoactive substance-induced organic mental conditions and of organic mental conditions associated with Axis III physical disorders. Dementia was also listed as a group of specific disorders, including primary degenerative dementia of the Alzheimer's type, multi-infarct dementia, dementia associated with alcoholism, and dementia not otherwise specified. A severity scale of mild, moderate, or severe was provided. DSM-IV eliminates the distinction between dementia as a syndrome and dementia as a disorder. Instead, it delineates those dementing disorders that are related to specific systemic medical or cerebral conditions (e.g., dementia of the Alzheimer's type and vascular dementia). DSM-IV criteria emphasize the defining features of dementia, namely the multiple deficits that represent a decline from a previously attained level of functioning, and incorporate specific information for distinguishing the etiological subcategories from each other, relying on course of the disease, the presence or absence of focal neurological signs and symptoms, laboratory evidence of neurological damage, a history of significant substance abuse, or other evidence of a contributing medical condition. Dementia of the Alzheimer's type is a diagnosis of exclusion, requiring that other potentially etiological CNS or systemic medical conditions be ruled out.

Beyond DSM-IV, there are alternative, conceptually overlapping systems for diagnosing dementia. ICD-10, in contrast to DSM-IV, maintains the approach adopted in DSM-III and DSM-III-R, with a general syndromic definition, which is then applied to specific disorders; for example, dementia in Alzheimer's disease or dementia in Huntington's disease. ICD-10 defines *dementia* as a syndrome in which:

> there is a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. Impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation . . . In assessing the presence or absence of a dementia, special care should be taken to avoid false-positive identification: motivational or emotional factors, particularly depression, in addition to motor slowness and general physical frailty, rather than loss of intellectual capacity, may account for failure to perform.

ICD-10 also states:

> Dementia produces an appreciable decline in intellectual functioning, and usually some interference with personal activities of daily living, such as washing, dressing, eating, personal hygiene, excretory and toilet activities. How such a decline manifests itself will depend largely on the social and cultural setting in which the patient lives. Changes in role performance, such as lowered ability to keep or find a job, should not be used as criteria of dementia because of the large cross-cultural differences that exist in what is appropriate, and because there may be frequent, externally imposed changes in the availability of work within a particular culture.

This latter statement differs fundamentally from DSM-IV. It underscores an unresolved controversy in the clinical and scientific literature where, in the absence of diagnostic tests for specific disease entities, clinicians and researchers look for sensitive indicators of onset and disease impact. Although ICD-10 explicitly eschews a functional performance criterion, its diagnostic guidelines for dementia then state: "The primary requirement for diagnosis is evidence of a decline in both memory and thinking which is sufficient to impair personal activities of daily living. The impairment of memory typically affects the registration, storage, and retrieval of new information, but previously learned and familiar material may also be lost, particularly in the later stages. Dementia is more than dysmnesia: there is also impairment of thinking and of reasoning capacity, and a reduction in the flow of ideas. The processing of incoming information is impaired, in that the individual finds it increasingly difficult to attend to more than one stimulus at a time, such as taking part in a conversation with several persons, and to shift the focus of attention from one topic to another. If dementia is the sole diagnosis, evidence of clear consciousness is required." Thus the central component outlined in ICD-10 is "a decline . . . sufficient to impair personal activities of daily living." Many investigators view this level of decrement as overly severe or too far progressed, potentially precluding use of newly available therapeutic agents until the degenerative process has advanced unnecessarily. Also, these distinctive approaches to diagnostic criteria underscore the potential for substantial variation between the results of studies employing one set versus the other. In the absence of a 'gold standard' test to externally validate one approach or the other, clinicians and investigators comparing research results must maintain a high degree of caution.

ICD-10 includes four dementia categories: (1) dementia in Alzheimer's disease; (2) vascular dementia; (3) dementia in diseases classified elsewhere in the ICD (e.g., dementia in Pick's disease, Huntington's disease, Parkinson's disease, Creutzfeldt-Jakob disease); and (4) unspecified dementia.

Another set of research criteria for the diagnosis of dementia of the Alzheimer's type, established by the National Institute of Neurological Communicative Diseases and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), now the Alzheimer's Association, has become known as the NINCDS-ADRDA criteria. Several studies have shown that a diagnosis of probable dementia of the Alzheimer's type according to NINCDS-ADRDA criteria selects patients similar to those diagnosed using DSM-III criteria. Depending on the case series, both criteria sets have been capable of identifying cases of Alzheimer's disease confirmed postmortem with a 70 to 90 percent specificity. The DSM-IV criteria share many features for the diagnosis of probable dementia of the Alzheimer's type but go beyond them to more clearly define important behavioral subtypes, akin to ICD-10, that may help guide symptomatic treatment interventions.

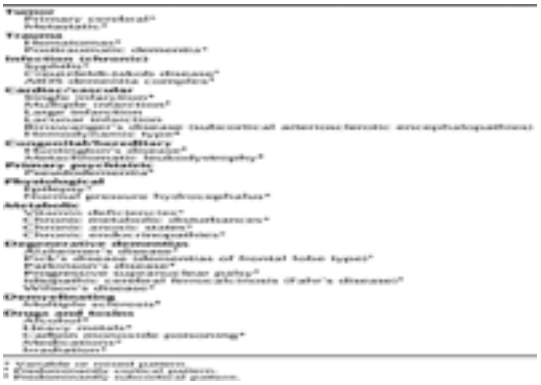
Recent critics regard the DSM-IV specifying phrase “with behavioral disturbance” as inadequate. Some advocate the enumeration of discrete subtypes of noncognitive neuropsychiatric syndromes to further classify the behavioral and psychological signs and symptoms found in patients with neurodegenerative dementing disorders. Whether such an approach will prove useful will depend upon defining more completely: (1) the presentation (i.e., form) of the clinical signs and symptoms that require treatment; (2) whether specific noncognitive neuropsychiatric syndromes exist as a central feature (although neither necessary nor sufficient diagnostically) of Alzheimer's disease or other diseases that cause dementia; (3) the prognostic significance of such symptoms, signs, or syndromes; (4) their pathobiological and causal substrates; (5) psychological, social, and environmental factors that affect their expression; and (6) their response(s) to specific therapeutic interventions.

**Epidemiology** The prevalence of dementia rises exponentially with age. The estimated prevalence of moderate to severe dementia in a population aged 65 years or older is consistently reported at approximately 5 percent. Within that age group the exponential curve is pronounced so that the prevalence in the subgroup aged 65 to 69 years is 1.5 to 2 percent; in the subgroup aged 75 to 79 years it is 5.5 to 6.5 percent; and in the subgroup aged 85 to 89 years it is 20 to 22 percent. Dementia of the Alzheimer's type is the most common dementing disorder in clinical and neuropathological prevalence studies reported from North America, Scandinavia, and Europe. Prevalence studies from Russia and Japan show vascular dementia to be more common in those countries. It remains unclear whether those apparent clinical differences reflect true etiological distinctions or inconsistent uses of diagnostic criteria. Dementia of the Alzheimer's type becomes more common with increasing age; among persons older than 75 years, the risk is six times greater than the risk for vascular dementia. There is a suggestion of higher rates of dementia of the Alzheimer's type in females and higher rates of vascular dementia in males. In geriatric psychiatric patient samples, dementia of the Alzheimer's type is a much more common etiology (50 to 70 percent) than vascular dementia (15 to 25 percent).

Studies of the incidence of dementia have been plagued by widely differing methodology and results. Again, there is an exponential increase in incidence with age, although some reports have noted a leveling off starting around age 75 years.

**Etiology** Table 10-27 lists common causes of dementia. Alzheimer's disease, the most common type of degenerative dementia, was discussed in an earlier section. Huntington's disease and Parkinson's disease were also discussed earlier in the chapter as paradigmatic examples of subcortical degenerative processes, with clinical and neuropathological descriptions separating them from cortical dementias. There may be clinical and neuropathological overlap between Alzheimer's disease and Parkinson's disease, especially among older patients. The significance of this finding remains unknown.

**Table 10-27** Causes of Dementia



**Frontal Lobe Degeneration** In recent years several authors have sought to distinguish dementias of the frontal lobe from other disorders. The uncertain status of dementias of the frontal lobe as distinct clinical and neuropathological entities has not yet warranted their formal inclusion in DSM-IV or ICD-10. They are described as cortical dementias that are found in as many as 10 to 20 percent of cases in some neuropathological series. Age at onset is apparently between 50 and 60 years for the majority, but the reported range is broad—20 to 80 years. The early clinical features of frontal lobe dementias are typified by damage to the frontal lobes and include prominent changes in personality and behavior. The personality changes include disinhibition, social misconduct, and lack of insight; these changes progress to apathy, mutism, and repetitive behaviors. A variant of the Kluver-Bucy syndrome, a condition originally described in monkeys that had undergone surgical ablation of the temporal lobes, is also described in the early stages of frontal lobe dementias and is characterized by combinations of disrupted eating behavior, hyperorality, mood disturbances, and sensory agnosias. Language, praxis, and gnosis are relatively spared early in the disease course, in contrast to dementia of the Alzheimer's type. However, dementias of the frontal lobe are described as progressive conditions that may in some cases involve memory as well as other cognitive functions. To date no studies have attempted to prospectively discriminate dementia of frontal lobe origin from dementia of the Alzheimer's type, with subsequent neuropathological confirmation to determine clinical diagnostic accuracy.

Neuropsychological testing in patients suspected of having dementia of frontal lobe origin may demonstrate disproportionate impairment in tasks related to frontal lobe function, such as deficiency in abstract thinking, attentional shifting, or set formation. Structural neuroimaging, such as CT or MRI, may reveal prominent atrophy of the frontal lobe, especially early in the disease process. Functional neuroimaging may prove more reliable for distinguishing dementia of frontal lobe origin from dementia of the Alzheimer's type. Regional cerebral blood flow studies using radioactively labeled xenon and SPECT studies have demonstrated disproportionate decreases in blood flow, radio tracer uptake, and glucose metabolism in the frontal lobes in patients with suspected or autopsy-confirmed frontal lobe dementia.

At present, the definitive diagnosis of any degenerative dementia rests on postmortem neuropathological examination. Only one type of frontal lobe dementia, Pick's disease, is associated with distinctive histopathological abnormalities that allow for certain diagnosis. Swollen neurons known as Pick cells and intraneuronal inclusions known as Pick bodies define the disorder neuropathologically (Fig. 10-12). Demyelination and gliosis of the frontal lobe white matter may also be found. Other frontal lobe

dementias have been referred to as dementia of the frontal lobe type or frontal lobe degeneration of non-Alzheimer's type. They have been distinguished from Alzheimer's disease by their marked gross morphological involvement of frontal and anterior temporal lobes, with relative sparing of the postcentral and temporoparietal areas mostly affected in Alzheimer's disease, and by the absence of amyloid plaques and neurofibrillary tangles microscopically. The lack of positive neuropathological inclusion criteria leaves many of these clinical conditions as disease entities of uncertain status, defined histopathologically by the absence of specific features. Whenever the hallmark findings of Alzheimer's disease are present, that diagnosis has been applied, irrespective of prior clinical findings. Thus, there are no data available to determine how many clinically diagnosed cases of frontal lobe dementia have been recast as Alzheimer's disease after death.

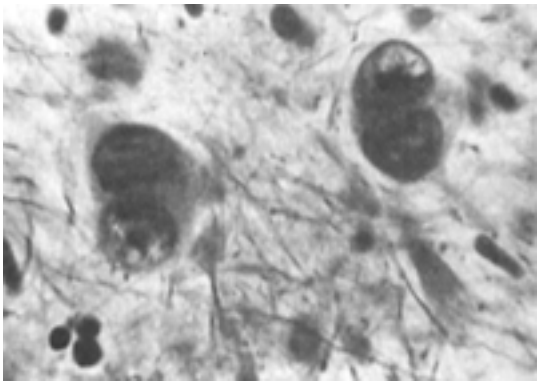


**FIGURE 10-12** Intraneuronal inclusions in Pick's disease. Silver stain. (Reprinted with permission from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, Baltimore, 1995.)

Of the potentially multiple forms of dementia associated with progressive frontal lobe dysfunction, only one type can be distinguished from Alzheimer's disease neuropathologically; the others show no defining postmortem signs. They may also be difficult to distinguish clinically in life. In the early stages of disease, the predominance of behavioral and personality disturbance, the presence of primitive reflexes, and neuropsychological and neuroimaging evidence of disproportionate frontal lobe involvement can help with a more confident premortem diagnosis of frontal lobe dementia. Some authors have assumed that there are many variants of dementia of frontal lobe origin that cannot be distinguished from each other clinically; at present, only Pick's disease has definitive neuropathological features.

**Subcortical Degeneration** Huntington's disease and Parkinson's disease were discussed earlier as examples of degenerative disorders with a subcortical pattern of deficits. *Progressive supranuclear palsy*, first described in 1964, is a degenerative disease involving the brainstem, cerebellum, and basal ganglia. The presenting history is usually notable for a gait disturbance, particularly spontaneous toppling. The clinical examination is notable for supranuclear paralysis of extraocular movements, particularly in the vertical plane. Dysarthria and dystonic rigidity of the neck and trunk are also common. Onset is usually after age 50 years, with progressive muscular rigidity. Neuropathology is notable for cell loss and gliosis of various nuclei in the brainstem, basal ganglia, and cerebellum, with striking preservation of the cortex. Progressive supranuclear palsy and Huntington's disease were the two disorders to which the label “subcortical dementia” was originally applied. In progressive supranuclear palsy a marked slowing of cognitive processes, apathy, and lack of initiative have been

described, associated with relative sparing of language, memory, and praxis. *Fahr's disease* involves idiopathic calcification of the basal ganglia. A subcortical dementia with a parkinsonian syndrome has been described. (Mild basal ganglia calcification is frequently observed incidentally on neuroimaging studies. The clinical significance of that finding is unknown.) Basal ganglia calcification can also be seen in patients with disorders of calcium metabolism, with the expected patterns of subcortical dementia and movement disorder.

**Vascular Etiologies** Cerebrovascular diseases together comprise the second most common cause of dementia. This category of dementia was referred to in the past as arteriosclerotic dementia, reflecting the belief that vascular insufficiency was responsible for the cognitive degeneration. That has now been supplanted by the belief that tissue damage or infarction underlies the vascular dementias. Cerebral infarction can be the result of a number of processes, of which thromboembolism from a large vessel plaque or cardiothrombus is the most common (Fig. 10-13). Anoxia due to cardiac arrest, hypotension, anemia, or sleep apnea can also produce ischemia and infarction. Cerebral hemorrhage related to hypertension or an arteriovenous malformation accounts for approximately 15 percent of cerebrovascular disease (Fig. 10-14).

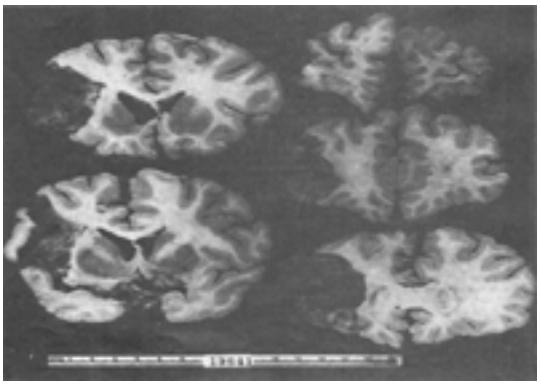


**FIGURE 10-13** Hemorrhagic infarct in the territory of the middle cerebral artery. (Reprinted with permission from Hirano A: *A Guide to Neuropathology*. Igaku-Shoin, New York, 1981.)

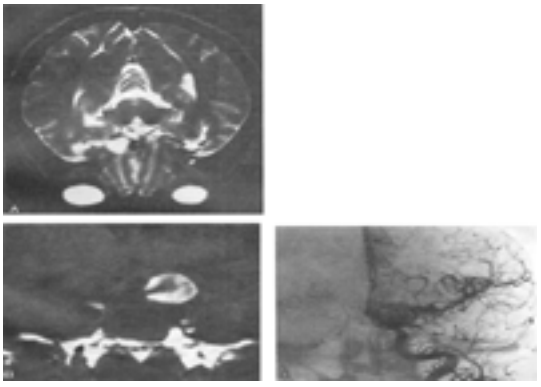


**FIGURE 10-14** Giant aneurysm. **A**, T2-weighted axial MRI scan shows a large, hyperintense mass in the left suprasellar region with medial displacement of the distal left internal carotid artery. **B**, T1-weighted coronal MRI scan demonstrates the heterogeneous parasellar mass; the areas of increased signal intensity indicate thrombus. A small curvilinear focus of flow void is seen medially most consistent with small residual patent vascular lumen. These findings are suggestive of partially thrombosed giant aneurysm. **C**, Anteroposterior view of arterial phase of left common carotid arteriogram illustrates a giant aneurysm of the left internal carotid artery. (Reprinted with permission from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, Baltimore, 1995.)

The clinical characteristics of a vascular dementia depend on the area of infarction. As such, there is a wide variability in the possible presenting features of a vascular dementia. Single infarctions may result in the discrete loss of one particular function (e.g., language) without dementia per se. However, some strategically located infarctions can affect more than one domain of cognitive function and mimic the clinical picture of a global dementia. An example is the angular gyrus syndrome that can occur with large posterior lesions in the dominant hemisphere. It has been characterized as manifesting with alexia with agraphia, aphasia, constructional disturbances, and Gerstmann syndrome (acalculia, agraphia, right-left disorientation, and finger agnosia). Although the findings are similar to those of dementia of the Alzheimer's type, angular gyrus syndrome can be distinguished by its abrupt onset, the presence of focal neurological, EEG, and imaging abnormalities, and preservation of memory and ideomotor praxis.

Vascular dementia is more commonly associated with multiple infarctions. The infarctions may take the form of numerous large infarctions accompanied by widespread cognitive and motor deficits. Tiny, deep infarctions, *lacunes*, result from disease of the small arteries that usually involves subcortical structures, such as the basal ganglia, thalamus, and internal capsule. The neurological and cognitive deficits may resolve quickly after each of the small strokes; however, the deficits may accumulate, leading to a persisting functional and intellectual decline. In the past a stepwise pattern of deterioration was described for that type of vascular dementia, but it was dropped from the DSM-IV criteria, as no specific pattern of deterioration has been reliably demonstrated for vascular dementias. Similarly, the description of patchy deficits has been deleted, in light of the marked variability in presentation of vascular dementia, depending on the type of vasculature and the site and extent of infarction.

**Binswanger's Disease** Also called subcortical arteriosclerotic encephalopathy, this is characterized by microinfarctions of the white matter with sparing of the cortex. It was originally believed to be a rare form of dementia that could be diagnosed only at autopsy. With the advent of sophisticated neuroimaging techniques such as CT and MRI and the common observation of white matter hyperintensities, there is renewed interest in the disease. Binswanger's disease produces a subcortical pattern of dementia, as the neuropathology is restricted to white matter. However, the mere presence of white matter hyperintensities on MRI is not adequate for diagnosis, as those areas may represent small infarctions, focal demyelination, or simply dilated perivascular spaces. Some studies have found no postmortem pathological correlate to white matter hyperintensities detected on MRI in vivo. Recently, criteria have been proposed for the diagnosis of Binswanger's disease that include clinical and neuropsychological confirmation of dementia, the presence of vascular risk factors, evidence of focal cerebrovascular disease, evidence of subcortical dysfunction, and bilateral white matter abnormalities greater than 2 mm in size on CT or T2-weighted MRI scans. Vascular dementia of the hemodynamic type is a classification that has been used to refer to cognitive impairments that arise secondary to hypotensive episodes, such as those due to cardiac dysrhythmias or hypotension. They may overlap phenomenologically with other conditions that result from chronic hypoxia.

*Wilson's disease* (*hepatolenticular degeneration*) is an inherited disorder involving abnormal metabolism of copper. Copper accumulates in both the liver and the CNS, particularly in the striatum, caudate, and putamen. Onset usually occurs during childhood or adolescence, although it may be

delayed until middle age. Personality change and behavioral disturbance are the most common neuropsychiatric manifestations (and frequently the presenting symptoms of the disease), but cognitive impairment may also be present. The latter takes the form of a subcortical dementia, with psychomotor slowing and loss of initiative, in the presence of relatively spared language functions, memory, and praxis. Motor symptoms are prominent in a parkinsonian pattern and include rigidity, tremor, and, at times, athetosis. The diagnosis is confirmed by assay of serum copper levels and urinary copper excretion. Treatment with chelating agents—dimercaprol (BAL); in the past and penicillamine (Cuprimine) more recently—can retard the progression of the disease and in some instances can result in improvement in clinical features. Neuropsychiatric symptoms are treated symptomatically.

**Other Causes** Primary psychiatric disorders can present with cognitive impairment. The term "pseudodementia" has been used to describe cognitive deficits that can be seen in the presence of idiopathic psychiatric illness, especially major depressive disorder. The deficits are usually subcortical in nature, involving attention, speed of mental processing, memory retrieval, and verbal fluency and elaboration. Patients may register new material but have difficulty with spontaneous recall that typically improves when they are presented with recognition cues. Pseudodementia was originally thought to be simply another expression of the depressed patient's lack of energy and unwillingness to attend to tasks. More recently, it has become clear that the deficits of pseudodementia represent fundamental cognitive deficits related to the same brain dysfunction that is responsible for the depressive symptoms. *Pseudodementia syndrome of depression* is one current term that is synonymous with *pseudodementia* and may more accurately reflect the nature of the pathobiological process. Recent studies have indicated that it may have a poorer prognosis, especially in the elderly, and several investigators have described a persistent mild anomia in the same patient population.

Schizophrenia was viewed at first as a disorder in which cognitive impairment was a prominent feature (dementia precox). Negative symptoms such as paucity of speech, poverty of ideas, blunting of affect, and functional deterioration contributed to that perception. Contemporary studies have demonstrated consistent cognitive deficits in certain subgroups of schizophrenia patients, primarily involving neuropsychological tasks thought to be sensitive to frontal lobe function. However, it is unclear whether those deficits are acquired over the course of the illness or represent cognitive skills that have never developed, consistent with the neurodevelopmental hypothesis of schizophrenia.

*Normal pressure hydrocephalus* is an idiopathic disorder caused by partial obstruction to the flow of CSF into the subarachnoid space. Onset typically occurs after age 60 years. The pathophysiology is thought to be related to disruption of neural function, either through stretching of periventricular fibers or through disruption of the pressure differential between the ventricular and subdural spaces, compromising neuronal function by altering cerebral blood flow. The classic clinical triad of dementia, incontinence, and gait disturbance is not present uniformly in all patients with normal pressure hydrocephalus, especially early in the course, although it nearly always emerges if the condition goes unrecognized or untreated. The diagnosis is based on clinical findings, neuroimaging evidence of ventricular dilation in the absence of sulcal widening (Fig. 10-15), and normal CSF pressure measurements on lumbar puncture. The dementia can be of a subcortical or cortical pattern and may at times be reversed with CSF shunt surgery. Specific indicators of a positive outcome remain to be

established, although identification of the etiology and a short disease course favor improvement in the dementia. Rarely, case reports have documented marked improvements up to 4 years after the onset of progressive dementia.

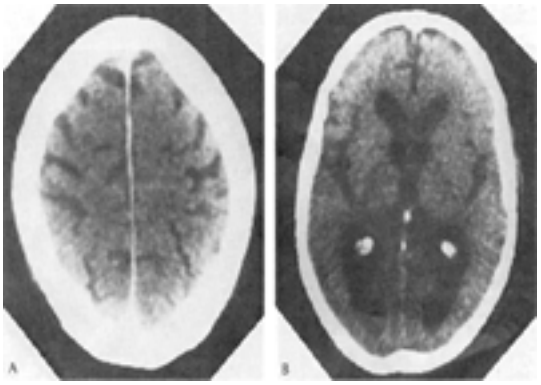


**FIGURE 10-15** Brain CT scans. Marked ventricular dilatation (**A**) and widening of cortical sulci (**B**) indicative of hydrocephalus ex vacuo in a 64-year-old woman with dementia. (Reprinted with permission from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, 1995.)

*Irradiation-induced dementia* is an iatrogenic concomitant of cranial radiation treatment that has been reported with greater frequency as the posttreatment survival time for patients with intracranial tumors has lengthened. Although transient cognitive deficits can be observed coincident with treatment or soon after treatment, a progressive irreversible dementia can begin 6 to 24 months after the termination of treatment. White matter is particularly sensitive to the deleterious effects of irradiation, and the dementia is predominantly subcortical in nature, reflecting the preferential white matter degeneration. The pathophysiology has been hypothesized to involve arteriolar leakage and localized edema.

## DIAGNOSIS AND CLINICAL FEATURES

DSM-IV has eliminated the general syndrome of dementia that was included in DSM-III-R. The dementia diagnoses in DSM-IV are dementia of the Alzheimer's type (Table 10-28), vascular dementia (Table 10-29), dementia due to other general medical conditions (Table 10-30), substance-induced persisting dementia (Table 10-31), dementia due to multiple etiologies (Table 10-32), and dementia not otherwise specified (Table 10-33). The ICD-10 diagnostic criteria for dementia are presented in Table 10-34, Table 10-35, Table 10-36, and Table 10-37.

**Table 10-28** DSM-IV Diagnostic Criteria for Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) one (or more) of the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g. multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.
D. The deficits do not occur exclusively during the course of a delirium.

Code based on predominant features:
**With delirium:** if delirium is superimposed on the dementia
**With delusions:** if delusions are the predominant feature
**With depressed mood:** if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.
**Uncomplicated:** if none of the above predominates in the current clinical presentation

Specify if:
**With behavioral disturbance**
**Coding note:** Also code cerebrovascular condition on Axis III.



**Table 10-29** DSM-IV Diagnostic Criteria for Vascular Dementia

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) one (or more) of the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of one of the general medical conditions listed below.
D. The deficits do not occur exclusively during the course of a delirium.

**Dementia due to HIV disease**
**Coding note:** Also code HIV infection on Axis III.
**Dementia due to head trauma**
**Coding note:** Also code head injury on Axis III.
**Dementia due to Parkinson's disease**
**Coding note:** Also code Parkinson's disease on Axis III.
**Dementia due to Huntington's disease**
**Coding note:** Also code Huntington's disease on Axis III.
**Dementia due to Pick's disease**
**Coding note:** Also code Pick's disease on Axis III.
**Dementia due to Creutzfeldt-Jakob disease**
**Coding note:** Also code Creutzfeldt-Jakob disease on Axis III.
**Dementia due to . . . (indicate the general medical condition not listed above)**
For example, normal pressure hydrocephalus, hypothyroidism, brain tumor, vitamin $B_{12}$ deficiency, intracranial radiation
**Coding note:** Also code the general medical condition on Axis III.



**Table 10-30** DSM-IV Diagnostic Criteria for Dementia Due to Other General Medical Conditions

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information and to recall previously learned information)
(2) one (or more) of the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. There is evidence from the history, physical examination, or laboratory findings that the deficits are etiologically related to the persisting effects of substance use (e.g., a drug of abuse, a medication).

Code: (Specific substance)-induced persisting dementia: (Alcohol; inhalant; sedative, hypnotic, or anxiolytic; other (or unknown) substance)



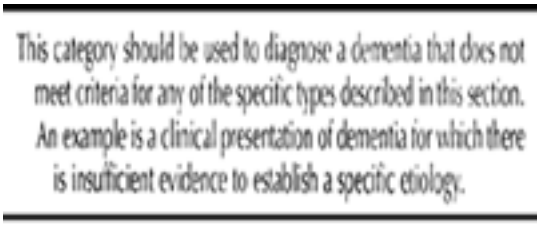
**Table 10-31** DSM-IV Diagnostic Criteria for Substance-Induced Persisting Dementia

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (inability to learn new information and to recall previously learned information)
(2) one (or more) of the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. There is evidence from the history, physical examination, or laboratory findings that the disturbance has more than one etiology (e.g., head trauma plus chronic alcohol use, dementia of the Alzheimer's type with the subsequent development of vascular dementia).
D. The deficits do not occur exclusively during the course of delirium.

**Coding note:** Use multiple codes based on specific dementias and specific etiologies, e.g., dementia of the Alzheimer's type, with late onset uncomplicated; vascular dementia, uncomplicated.



**Table 10-32** DSM-IV Diagnostic Criteria for Dementia Due to Multiple Etiologies



This category should be used to diagnose a dementia that does not meet criteria for any of the specific types described in this section. An example is a clinical presentation of dementia for which there is insufficient evidence to establish a specific etiology.



**Table 10-33** DSM-IV Diagnostic Criteria for Dementia Not Otherwise Specified

**Table 10-34** ICD-10 Diagnostic Criteria for Dementia

**Table 10-35** ICD-10 Diagnostic Criteria for Dementia in Alzheimer's Disease

**Table 10-36** ICD-10 Diagnostic Criteria for Vascular Dementia

**Table 10-37** ICD-10 Diagnostic Criteria for Dementia in Other Diseases Classified Elsewhere

**Dementia of the Alzheimer's Type** The DSM-IV diagnostic criteria for dementia of the Alzheimer's type emphasize the presence of memory impairment and the associated presence of at least one other symptom of cognitive decline (aphasia, apraxia, agnosia, or abnormal executive functioning). The diagnostic criteria also require a continuing and gradual decline in functioning, impairment in social or occupational functioning, and the exclusion of other causes of dementia. DSM-IV suggests that the age of onset be characterized as early (at age 65 or below) or late (after age 65) and that a predominant behavioral symptom be coded with the diagnosis, if appropriate.

**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 the presence of either clinical or laboratory evidence supportive of a vascular cause of the dementia.

**Dementia Due to Other General Medical Conditions** DSM-IV lists six specific causes of dementia that can be coded directly: HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, and Creutzfeldt-Jakob disease. A seventh category allows the clinician to specify other nonpsychiatric medical conditions associated with dementia.

**Substance-Induced Persisting Dementia** The primary reason that this DSM-IV category is listed both with the dementias and with the substance-related disorders is to facilitate the clinician's thinking regarding differential diagnosis. The specific substances that DSM-IV cross-references are alcohol; inhalant; sedative, hypnotic, or anxiolytic; and other or unknown substances.

**Clinical Diagnosis and Evaluation** The first step in the diagnosis of dementia is to establish that the cognitive deficits have occurred in a patient with a stable level of consciousness, without fluctuation or waxing and waning. It must also be demonstrated that the patient has multiple deficits rather than a focal disturbance such as that seen in amnestic disorder or primary progressive aphasia (the insidious onset of a slowly progressive language disturbance with relatively preserved memory, reasoning, judgment, and comportment). Once the basic criteria for the diagnosis of dementia have been met, the task is to determine which etiology is responsible by using the standard means of history, clinical examination, and laboratory evaluation.

A 61-year-old high-school science department head, who was an experienced and enthusiastic camper and hiker, became extremely fearful while on a trek in the mountains. Gradually, over the next few months he lost interest in his usual hobbies. Formerly a voracious reader, he stopped reading. He had difficulty doing computations and made gross errors in home financial management. On several occasions he became lost while driving in areas that were formerly familiar to him. He began to write notes to himself so that he would not forget to do errands. Very abruptly, and in uncharacteristic fashion, he decided to retire from work, without discussing his plans with his wife. Intellectual deterioration gradually progressed. He spent most of the day piling miscellaneous objects in one place and then transporting them to another spot in the house. He became stubborn and querulous. Eventually he required assistance to shave and dress.

When examined 6 years after the first symptoms had developed, the patient was alert and cooperative. He was disoriented with respect to place and time. He could not recall the names of four or five objects after a 5-minute interval of distraction. He could not remember the names of his college and graduate school or the subject in which he had majored. He could describe his job by title only. In 1978 he thought that John Kennedy was president of the United States. He did not know Joseph Stalin's nationality. His speech was fluent and well articulated, but he had considerable difficulty finding words and used many long and essentially meaningless phrases. He called a cup a vase, and identified the rims of glasses as “the holders.” He did simple calculations poorly. He could not copy a cube or draw a house. His interpretation of proverbs was concrete, and he had no insight into the nature of his disturbance.

An elementary neurological examination revealed nothing abnormal, and routine laboratory tests were also negative. A CT scan, however, showed marked cortical atrophy. (Reprinted with permission from *DSM-IV Casebook*.)

For dementia of the Alzheimer's type, a family history of the dementia is probably the most important risk factor after advanced age. A family history of Down syndrome or of hematological malignancies, such as leukemia, myelolymphoma, or Hodgkin's disease, is also associated with an increased risk for Alzheimer's disease. There is some evidence for a familial predisposition to vascular dementia, but it has not been demonstrated as clearly as for dementia of the Alzheimer's type. The family history is of greatest significance in the heredity dementias, such as Huntington's disease, which is transmitted via a single autosomal dominant gene with nearly 100 percent penetrance. A history of a parent or grandparent with a movement disorder and dementia should alert the clinician to that diagnostic possibility. Huntington's disease does not skip generations, although family members may have died from other causes prior to the emergence of definable symptoms. A familial pattern has been established for Wilson's disease, with a presumptive autosomal recessive gene responsible for abnormal copper metabolism. Metachromatic leukodystrophy similarly is inherited in a recessive pattern with incomplete penetrance.

Degenerative dementias as a group do not have well-established risk factors other than old age and familial patterns. For dementia of the Alzheimer's type, other risk factors identified tentatively in recent

years include female sex, a past history of head trauma, and lower education. Vascular dementias are highly associated with the risk factors for cerebrovascular disease. Those factors include hypertension (especially with systolic pressures greater than 160 mmHg), cardiac disease, transient ischemic attacks, diabetes mellitus, carotid bruits, and sickle cell disease. Obesity, a sedentary lifestyle, tobacco use, alcohol consumption, and elevated serum cholesterol and lipid levels are less well established as risk factors for cerebrovascular disease.

A history of severe head trauma or multiple traumas over a period of time (such as in boxers) should raise the suspicion of dementia related to brain trauma. Although severe head trauma earlier in life increases the risk of dementia of the Alzheimer's type, its mechanism of action is unknown. A history of an untreated or partially treated sexually transmitted disease should raise the suspicion for neurosyphilis. The presence of risk factors for HIV infection, namely homosexuality, multiple sexual partners, and intravenous drug use, similarly increase the risk for dementia due to HIV disease. Patients with chronic medical illnesses, especially if poorly controlled, such as epilepsy, renal failure, or hepatic cirrhosis, are also at greater risk for developing dementias. A history of occupational exposure to heavy metals or other toxins should be obtained as part of any evaluation for dementia.

**Pathology and Laboratory Examination** 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 diseases. Frontal release signs and primitive reflexes, while suggesting pathology in the frontal lobe, are present in many disorders and often point to a greater extent of progression.

Laboratory evaluation can assist in definitive identification of the etiological agent. The range of possible etiologies 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. Table 10-4 lists a number of laboratory tests useful in evaluating specific diseases presenting as dementia.

**Differential Diagnosis** The first step in the diagnosis of dementia is to exclude delirium. Delirium can mimic every possible psychiatric disorder and symptom. It is most common in the same populations in which dementia is most common, namely the elderly and the brain-injured. It can be distinguished from dementia by its cardinal feature, disturbance of consciousness. Level of consciousness or arousal must be determined to be stable before a diagnosis of dementia can be made with confidence. Dementia must also be distinguished from focal or specific cognitive impairments, such as those seen in aphasic or amnestic patients. Mood disorders can present with cognitive symptoms, particularly in the dementia of depression or pseudodementia. A history of a mood disorder or a current disturbance in neurovegetative function should alert the clinician to the possibility of a major depressive disorder.

**Course and Prognosis** The course and prognosis of a dementia syndrome vary with its cause. Dementia does not in itself imply a progressive deterioration, although many of the pathobiological processes underlying dementia are degenerative, and there is no known means of altering the progressive clinical deterioration. The rate of progression may vary within families or from individual to individual. Occasionally, progression can be halted or slowed in the vascular dementias if contributing risk factors for further vascular events can be reduced. Some dementias, such as those related to endocrine or metabolic processes or drug intoxications, may resolve entirely with the treatment or with removal of the basic disorder. However, a long-standing cerebral insult often leads to chronic clinical deficits that persist even when the insult has been removed. Dementias related to tumor and infection usually follow a similar pattern.

Age at onset is an important feature of any illness. Alzheimer's disease is the most common cause of dementia in the United States. Onset usually occurs after age 60 years and the prevalence increases exponentially with each successive decade, although cases have been reported in patients as young as 30 years. Familial forms of dementia of the Alzheimer's type appear to have an earlier age at onset. Cerebrovascular disease, the second most common cause of dementia, is associated with an earlier age at onset overall. Dementia secondary to other medical conditions usually arises only after the disease has progressed for some time. This observation is true of the dementias associated with infectious, physiological, metabolic, and toxic processes. The age at onset of Huntington's disease is usually between 30 and 50 years, but onset may occur earlier or later.

The dementias can be distinguished to some extent by their course, especially earlier in the disease process. Degenerative dementias are insidious in onset and gradually progressive. Despite the clinical rule of a steadily progressive course in dementia of the Alzheimer's type, some individuals may reach a plateau for several years in the overall functional impairment before progression resumes and continues on to death. Vascular dementias may follow a stepwise pattern, in which new deficits appear abruptly and associated with new vascular events, but the vascular dementias also often have an insidious onset and a slow but steadily progressive course. Dementias related to infection are usually acute, although syphilis and cryptococcal meningitis can have an indolent course. Metabolic dementias may begin rapidly or slowly, depending on the underlying systemic disease; correction of the basic deficiency or disturbance may result in improvement, although the cognitive deficits often persist. Drug- or toxin-related dementias may improve once the insult has been discontinued, although radiation-induced dementia is an exception: It first manifests many months after radiation exposure has ceased, and a progressive course ensues.

**Treatment** The first step in the treatment of dementia is verification of the diagnosis. Accurate diagnosis is imperative, for 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, as that has been demonstrated to improve cognitive function in patients with vascular dementia. Blood pressure below the normal range has been demonstrated to result in further impairment of cognitive function in the patient with dementia. The choice of antihypertensive

agent can be significant in that beta-blocking agents have been associated with exaggeration of cognitive impairment. Angiotensin-converting enzyme (ACE) inhibitors and diuretics have not been linked to the exaggeration of cognitive impairment and are thought to lower blood pressure without affecting cerebral blood flow (cerebral blood flow is presumed to correlate with cognitive function). Surgical removal of carotid plaques may prevent subsequent vascular events in carefully selected patients.

For the degenerative dementias, no direct therapies have been demonstrated conclusively to reverse or retard the fundamental pathophysiological processes. The search for such an agent has been exhaustive and fraught with frustration. Such studies are constructed on a growing foundation of knowledge regarding brain neurochemistry and the derangements found in dementia. Numerous neurotransmitters, including acetylcholine, dopamine, norepinephrine, GABA, and serotonin, and several neuropeptides, including somatostatin and substance P, are decreased in dementia. Alzheimer's disease has been studied the most extensively, but similar decreases in neurotransmitters have been found in Huntington's disease, alcohol–induced persisting dementia, vascular dementia, Parkinson's disease, and (rarely) in normal aging. Multiple neuropharmacological strategies have been devised in the hope of replenishing the deficient neurotransmitters. Replacement therapy for acetylcholine has been the most common and widely publicized strategy. Efforts at replenishment have included the use of acetylcholine precursors (e. g., example, choline [Anthropan] and lecithin [Phoschol]), cholinergic agonists (e.g., pilocarpine [Salagen] and arecoline), and cholinesterase inhibitors. Treatment with physostigmine (Antilirium, Eserine), a short-acting cholinesterase inhibitor, has consistently resulted in small but statistically significant improvements in memory in patients with dementia of the Alzheimer's type and in healthy control subjects during brief-duration infusion studies. New, longer-acting forms now are being investigated. Tacrine (Cognex), became the focus of public debate after a 1986 study reported alleged marked improvements in 16 patients with dementia of the Alzheimer's type. That study, however, was criticized for substantial methodological limitations and was not replicated in several subsequent attempts. Two multicenter studies of varying design were published in late 1992. One study, with an enriched population, aimed to maximize detection of beneficial effect, but found only marginal improvement and no overall evidence of clinically meaningful change. The second reported statistically significant but still modest improvements in cognition. The Food and Drug Administration (FDA) eventually approved the use of tacrine as a therapeutic agent for dementia of the Alzheimer's type. Clinicians must be aware of both its limited demonstrated benefit and its hepatotoxic potential.

Recently the FDA approved the cholinesterase inhibitor, donepezil (Aricept), for symptomatic treatment of mild to moderate cognitive deficits in patients with presumed Alzheimer's disease. Therapeutic effects have been modest. Dosages of 5 to 10 mg daily were given in experimental trials; common adverse effects have included nausea, diarrhea, and vomiting. Insomnia, muscle cramps, and anorexia have occurred occasionally, but unlike tacrine, so far there has been no reported hepatotoxicity. In summary, it has become clear that there are therapies available that may improve the function of patients with dementia of the Alzheimer's type without incurring severe toxicity. Thus it now seems reasonable to declare “When in doubt, treat!” This reflects a fundamental shift in the care of these individuals, moving beyond long-held nihilism to a more optimistic view of clinical intervention. It is the first step in a treatment revolution that will reach full force during the next 10 to 15 years.

Other experimental approaches to treating cognitive impairment or disease progression include a plant extract of *Ginkgo biloba*, estrogens, vitamin E, and prednisone (Deltasone, Orasone). Many researchers have concluded that the notion of a single or selective neurotransmitter defect for any specific dementing illness is simplistic and that future research efforts should be directed toward neuronal protection and regeneration. Selegiline (Eldepryl), a monoamine oxidase (MAO) type B (MAOB) inhibitor, has apparently slowed the progression of Parkinson's disease, presumably by limiting endogenous generation of destructive oxidative products. Similar antioxidant treatments are being used experimentally with other dementias, including Huntington's disease and vascular dementia. Naloxone (Narcan), an opiate antagonist, is thought to have possible application in vascular dementia based on animal studies in which it was demonstrated to decrease the sequelae of cerebral ischemia. Nerve growth factor is being studied as a means of promoting neural regeneration or sprouting.

The absence of curative therapies does not preclude efforts to ameliorate disturbing clinical problems. Symptomatic measures are the rule for behavioral management of most dementia syndromes. Programs that emphasize a high degree of regularity and consistency in daily schedule and environment can mitigate the risk of development of catastrophic reactions or explosive outbursts. All pharmacological agents that are used for the idiopathic psychiatric disorders can be used in patients with dementia, although usually at dosages one half to two thirds lower. Antidepressant medications and ECT are safe and effective for significant depressive symptoms. The use of antipsychotic should be restricted to patients with defined psychotic symptoms because patients with dementia are more susceptible to the parkinsonian adverse effects inherent in these agents. Clinicians and researchers are now cautiously using newer atypical antipsychotic drugs, seeking to avoid these adverse effects. Benzodiazepines may be used briefly and judiciously for emergency sedation but otherwise should be avoided because they can produce delirium and tend to further compromise residual cognitive capacities. Lithium (Eskalith), centrally active β-adrenergic blockers, carbamazepine (Tegretol), and valproate (Depakene) have been used empirically in the treatment of affective lability and aggressive outbursts. Empirical management therapies should be used in conjunction with environmental modifications. Individual psychotherapy may have benefit for patients in the early stages of dementia, especially to assist them in coping with their losses. The positive effects of a therapeutic relationship can still be felt at later stages when patients have more severe cognitive deficits. Family education and support are vital components of any treatment approach, as all members benefit from extensive knowledge about course and prognosis, as well as needing assistance when assuming new roles in their relationships with the patient.

**Amnestic Disorders** The inclusion of amnestic disorders in the psychiatric nosology reflects the classification's roots as a manual for state hospital or asylum patients. The number of individuals given amnestic diagnoses due to nutritional deficiency, often related to chronic alcohol dependence, has declined. In contrast, traumatic causes have increased dramatically during recent decades.

**Definition** The essential feature of amnestic disorders is the acquired impaired ability to learn and recall new information, coupled variably with the inability to recall previously learned knowledge or past events. The impairment must be sufficiently severe to compromise personal, social, or occupational functioning. The diagnosis is not made if the memory impairment exists in the context of reduced ability to maintain and shift attention, as encountered in delirium, or in association with significant functional

problems due to the compromise of multiple intellectual abilities, as seen in dementia. Amnestic disorders are secondary syndromes caused by systemic medical or primary cerebral diseases, substance use disorders, or medication adverse effects, as evidenced by findings from clinical history, physical examination, or laboratory examination.

**History and Comparative Nosology** Although amnestic disorder has been long described, its specific recognition has been relatively recent. It was most clearly elaborated by Sergei Korsakoff and was included among the alcoholic psychoses in DSM-I and DSM-II, as well as in earlier editions. In DSM-I it was classified under chronic brain syndrome associated with intoxication. Understanding that *psychosis* was the term used to denote more severe disturbances of mental status, the authors of DSM-I stated: “The latter [severe alcohol-related brain damage] may manifest itself by the type of chronic delirium formerly diagnosed as Korsakoff's psychosis.” Specific discussion of the amnestic syndromes was absent. Like DSM-I, DSM-II provided little clinical description of amnestic disorders, although a slightly longer definition was presented in the text.

> DSM-III and DSM-III-R, in contrast, provided an in-depth discussion and more specific diagnostic criteria. However, both volumes failed to underscore the essential quality of amnestic disorder as characterized by a specific cognitive deficit in the realm of memory, while dementia syndromes were reflective of multiple failures, including memory and other impaired intellectual abilities. DSM-III and DSM-III-R required “demonstrable evidence of impairment in both short- and long-term memory,” whereas the key feature of the disorder is an inability to learn and later recall new information. In addition, neither DSM-III nor DSM-III-R provided for the separation of transient from persistent amnesia. ICD-10 maintains the approach of DSM-III.

**Epidemiology** Data are not available for estimating the point or lifetime prevalence, incidence, or lifetime risk of persistent amnestic disorder. One recent study indicated that transient global amnesia may have an incidence of 5.2 cases per 100,000 population per year. There are no specific data available on age at onset or culture- or sex-related aspects beyond those relating to the genesis of primary etiological disease processes. For example, transient global amnesia typically occurs after age 50 years.

**Etiology** Amnestic disorder often occurs as the result of pathological processes that cause damage to specific diencephalic and middle temporal lobe structures (e.g., mammillary bodies, the hippocampus). The pathology is commonly bilateral, but deficits may arise from unilateral lesions. Pathogenic processes include closed-head trauma and penetrating missile wounds, focal tumors, surgical intervention, encephalitis due to infection from herpes simplex virus, infarction of the territory of the posterior cerebral artery, and hypoxia. A common cause of amnestic disorder is the chronic use of alcohol and associated thiamine deficiency.

Transient amnestic disorder, when encountered as a transient global amnesia, is typically associated with cerebrovascular disease and pathology in the vertebrobasilar system. Transient amnesia may also arise from episodic physiological or metabolic disorders, such as acute intoxications or seizures.

## DIAGNOSIS AND CLINICAL FEATURES

**Diagnosis** The differentiation between amnestic syndrome and amnestic disorder made in DSM-III-R has been eliminated in DSM-IV. For the diagnosis of amnestic disorder, DSM-IV requires the "development of memory impairment as manifested by impairment in the ability to learn new information or the inability to recall previously learned information," and the "memory disturbance causes significant impairment in social or occupational functioning." A diagnosis of amnestic disorder due to a general medical condition (Table 10-38) is made when there is evidence of a causatively relevant specific medical condition (including physical trauma). DSM-IV further categorizes the diagnosis as being transient or chronic. A diagnosis of substance-induced persisting amnestic disorder is made when there is evidence that the symptoms are causatively related to the use of a substance (Table 10-39). DSM-IV refers the clinician to specific diagnoses within substance-related disorders: alcohol-induced persisting amnestic disorder; sedative, hypnotic, or anxiolytic-induced persisting amnestic disorder; and other (or unknown) substance-induced persisting amnestic disorder. DSM-IV also provides for the diagnosis of amnestic disorder not otherwise specified (Table 10-40). The ICD-10 diagnostic criteria for organic amnesia syndrome not induced by alcohol and other psychoactive substances are listed in Table 10-41.

A. The development of memory impairment as manifested by impairment in the ability to learn new information or the inability to recall previously learned information.
B. The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.
C. The memory disturbance does not occur exclusively during the course of a delirium or a dementia.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition (including physical trauma).

*Specify if:*
**Transient:** if memory impairment lasts for 1 month or less
**Chronic:** if memory impairment lasts for more than 1 month

**Coding note:** Include the name of the general medical condition on Axis I, e.g., amnestic disorder due to head trauma; also code the general medical condition on Axis III.



**Table 10-38** DSM-IV Diagnostic Criteria for Amnestic Disorder Due to a General Medical Condition

A. The development of memory impairment as manifested by impairment in the ability to learn new information or the inability to recall previously learned information.
B. The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.
C. The memory disturbance does not occur exclusively during the course of a delirium or a dementia and persists beyond the usual duration of substance intoxication or withdrawal.
D. There is evidence from the history, physical examination, or laboratory findings that the memory disturbance is etiologically related to the persisting effects of substance use (e.g., a drug of abuse, a medication).

*Code:* (Specific substance)-induced persisting amnestic disorder: (Alcohol; sedative, hypnotic, or anxiolytic; other [or unknown] substance)



**Table 10-39** DSM-IV Diagnostic Criteria for Substance-Induced Persisting Amnestic Disorder

This category should be used to diagnose an amnestic disorder that does not meet criteria for any of the specific types described in this section.

An example is a clinical presentation of amnesia for which there is insufficient evidence to establish a specific etiology (i.e., dissociative, substance induced, or due to a general medical condition).



**Table 10-40** DSM-IV Amnestic Disorder Not Otherwise Specified

A. There is memory impairment, manifest in both
   1. A defect of recent memory (impaired learning of new material) to a degree sufficient to interfere with daily living
   2. A reduced ability to recall past experiences
B. There is no
   1. Defect in immediate recall (as tested, for example, by the digit span)
   2. Clouding of consciousness and disturbance of attention. Delirium, not induced by alcohol and other psychoactive substances
   3. Global intellectual decline (dementia)
C. There is objective evidence (from physical and neurological examination, laboratory tests) and/or history of an insult to, or a disease of the brain (especially, involving bilaterally the diencephalic and medial temporal structures but other than alcohol encephalopathy) that can reasonably be presumed to be responsible for the clinical manifestations

Comments. Associated features, including confabulations, emotional changes (apathy, lack of initiative), and lack of insight are useful additional pointers to the diagnosis but are not invariably present.



**Table 10-41** ICD-10 Diagnostic Criteria for Organic Amnesic Syndrome, Not Induced by Alcohol and Other Psychoactive Substances

**Clinical Features** The inability to learn and recall new information, the cardinal feature of the disorder, is most apparent on spontaneous, unstructured recall tasks but is also evident on tasks that provide recall cues or recognition paradigms where the stimulus is presented again, often among mnemonically equivalent distractor items. Depending on lesion localization, deficits may be predominantly related to verbal or visual stimuli. (Studies have demonstrated repeatedly that individuals with amnestic disorder may learn how to perform novel procedures that are not mediated verbally, such as motor tasks, even though they later fail to recall having had those learning experiences.)

Problems remembering previously learned materials are present variably among amnestic patients. For example, a patient who suffered traumatic brain damage and who continues to exhibit deficits in new learning may remember events up to a time shortly before the injury. In some cases the interval of preinjury recall impairment may diminish as the patient recovers (shrinking retrograde amnesia), where inaccessible memories from several years before the injury are gradually produced and the extent of the amnesia diminishes in the context of clinical improvement. Recall deficits due to other causes may involve memory for knowledge and events gained over many years' duration.

For some forms of amnestic disorder, events from the remote past may be better remembered than more recent events. However, such a gradient of recall is not present uniformly among individuals with amnestic disorders. Typically, the ability to immediately repeat a sequential string of information (e.g., a digit span) is not impaired in amnestic disorder; when such impairment is evident, it suggests the presence of attentional dysfunction that may be indicative of delirium. Amnestic disorders may be transient, lasting for several hours to a few days, as in transient global amnesia, or persistent, lasting at

least 1 month. In the context of a newly developed but unresolved memory impairment, the term *provisional* should be added to a diagnosis of transient amnesia.

*Transient global amnesia* is a form of transient amnestic disorder associated with episodes that are characterized by a dense, transitory inability to learn new information (i.e., to form sustained memories), with a variable (ultimately shrinking on recovery) inability to recall events that occurred during the duration of the disturbance. The episode is followed by restoration to a completely intact cognitive state. There are no data to suggest that the memory impairment is associated with disturbed or abnormal behavior beyond the mild confusion or perplexity that may be manifest during the episode.

Depending on the cause of the disorder, the onset of amnesia may be sudden or gradual. Head trauma, vascular events, or specific types of neurotoxic exposure (e.g., carbon monoxide poisoning) may lead to acute mental status changes. Prolonged substance abuse, chronic neurotoxic exposure, or sustained nutritional deficiency exemplify conditions that may lead to an insidious memory decline, eventually causing a clinically definable cognitive impairment.

Amnestic disorder may develop as a result of alcohol dependence, associated with dietary and vitamin deficiency. Alternatively, it may be the primary clinical deficit arising from traumatic head injury and may present as the major feature of a postconcussional state. When memory dysfunction exceeds other features of a postconcussional syndrome, it is preferable to diagnose the condition as amnestic disorder due to head trauma.

Although persons with amnestic disorders may manifest other features of the primary systemic or cerebral disease that cause the development of the memory impairment, disordered mental status may be the sole presenting feature. Thus, a clinician may misconstrue the history of a blandly confabulating person unless other corroborating persons are available. When amnestic disorder is the result of alcohol dependence and vitamin deficiency, other neurological complications of alcohol ingestion and malnutrition such as peripheral neuropathy and cerebellar ataxia, may be observed.

A 46-year-old house painter is admitted to the hospital with a history of 30 years of heavy drinking. He has had two previous admissions for detoxification, but his family states that he has not had a drink in several weeks, and he shows no signs of alcohol withdrawal. He looks malnourished, however, and on examination is found to be ataxic and to have a bilateral sixth cranial nerve palsy. He appears confused and mistakes one of his physicians for a dead uncle.

Within a week the patient walks normally, and there is no longer any sign of a palsy. He seems less confused and can now find his way to the bathroom without direction. He remembers the names and birthdays of his siblings, but has difficulty naming the past five United States presidents. More strikingly, he has great difficulty in retaining information for longer than a few minutes. He can repeat a list of numbers immediately after he has heard them, but a few minutes later does not recall being asked to perform the task. Shown three objects (keys, comb, ring), he cannot recall them 3 minutes later. He does not seem worried about this. Asked if he can recall the

name of his doctor, he replies, “Certainly,” and proceeds to call the doctor “Dr. Masters” (not his name), whom, he claims, he first met during the Korean War. He tells a long untrue story about how he and “Dr. Masters” served as fellow soldiers.

The patient is calm, alert, and friendly. Because of his intact immediate memory and spotty but sometimes adequate remote memory, one can be with him for a short period and not realize he has a severe memory impairment. Although treated with high doses of thiamine, the short-term memory deficit persists and appears to be irreversible. (Reprinted with permission from *DSM-IV Casebook*.)

**Pathology and Laboratory Examination** Laboratory findings diagnostic of the disorder may be obtained using quantitative neuropsychological testing. Standardized tests also are available to assess recall of well-known historical events or public figures, to characterize the nature of 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. However, memory deficits 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. However, damage of middle-temporal lobe structures is common and may be reflected in enlargement of third ventricle or temporal horns or in structural atrophy detected on MRI.

**Differential Diagnosis** The central feature of amnestic disorder is the inability to learn and recall new information, in the context of variable difficulties recalling previously learned factual knowledge. Less efficient memory is a component of normatively defined age-related cognitive decline but is neither functionally impairing nor below the statistically normal range when assessed with quantitative procedures. Patients with amnesia uniformly show significant abnormalities on cognitive or neuropsychological tests. Disordered memory is also a feature of delirium and dementia. When memory dysfunction occurs in the context of impaired consciousness, with reduced ability to focus, sustain, or shift attention, delirium predominates. The coexistence of memory impairment and multiple cognitive deficits (e.g., aphasia, apraxis, agnosis, and disturbance in executive functioning) warrants the diagnosis of dementia. Confabulation is a mental status finding encountered in patients with dementia as well as amnesia.

Amnestic disorder may emerge from an evolving clinical picture that includes confusion and disorientation, occasionally with attentional problems that suggest delirium. For example, classically described Korsakoff's syndrome has been associated most often with the delirium of Wernicke's encephalopathy. The latter typically clears quickly with appropriate treatment. Confabulation may be noted during the early stages of the disease process and is often indicated by the recitation of imaginary events to fill gaps in memory, but that sign tends to disappear with time. Profound amnesia typically is associated with disorientation to place and time but rarely to person. Disorientation to self may be encountered in patients with severe dementing disturbances characterized by multiple cognitive deficits but is atypical of pure amnestic disorder. Many patients with severe amnestic disorder lack insight into

their deficits, and they explicitly deny its presence despite evidence to the contrary. The lack of insight may contribute to accusations or agitation in rare instances. More commonly, apathy, lack of initiative, emotional blandness, or other changes suggestive of altered personality function may be encountered. Individuals may be superficially friendly or agreeable, but they frequently have a shallow or diminished range of affective expression. Patients with transient global amnesia most often appear bewildered or befuddled. Although they have been described participating in complex activity or conversations in the course of an episode, that is a much less common presentation.

Occasionally, patients may demonstrate intact abilities to learn new information associated with profound memory loss for a circumscribed period of time. That pattern occurs in the setting of a discrete (time-limited) process that temporarily interferes with the patient's ability to establish new memories. Such processes include acute intoxication, transient delirium or encephalopathy (e.g., a seizure), or some other transient disruption of cerebral functioning (e.g., a transient ischemic attack). Such transient amnestic episodes must be defined clinically in the context of the primary disease processes; failure to establish a primary systemic or cerebral etiology suggests a psychogenic origin when that symptom pattern is encountered.

Dissociative amnesia typically does not involve deficits in learning and recalling new information; rather, patients present with a circumscribed inability to recall previously learned information while they continue to function normally in the present.

Psychiatric consultation is requested by an emergency room physician on an 18-year-old male who has been brought into the hospital by the police. The youth appears exhausted and shows evidence of prolonged exposure to the sun. He identifies the current date incorrectly, giving it as September 27 instead of October 1. It is difficult to get him to focus on specific questions, but with encouragement he supplies a number of facts. He recalls sailing with friends, apparently about September 25, on a weekend cruise off the Florida coast, when bad weather was encountered. He is unable to recall any subsequent events and does not know what became of his companions. He has to be reminded several times that he is in a hospital, as he expresses uncertainty as to his whereabouts. Each time he is told, he seems surprised.

There is no evidence of head injury or dehydration. Electrolytes and cranial nerve examination are unremarkable. Because of the patient's apparent exhaustion, he is permitted to sleep for 6 hours. Upon awakening, he is much more attentive, but is still unable to recall events after September 25, including how he came to the hospital. There is no longer any doubt in his mind that he is in the hospital, however, and he is able to recall the contents of the previous interview and the fact that he had fallen asleep. He is able to remember that he was a student at a southern college, maintained a B average, had a small group of close friends, and has a good relationship with his family. He denies any previous psychiatric history and says he has never abused drugs or alcohol.

Because of the patient's apparently sound physical condition, a sodium amytal interview is performed. During this interview he relates that neither he nor his companions were particularly

experienced sailors capable of coping with the ferocity of the storm they encountered. Although he had taken the precaution of securing himself to the boat with a life jacket and tie line, his companions had failed to do this and had been washed overboard in the heavy seas. He completely lost control of the boat and felt he was saved only by virtue of good luck and his lifeline. He had been able to consume a small supply of food that was stowed away in the cabin over a 3-day period. He never saw either of his sailing companions again. He was picked up on October 1 by a Coast Guard cutter and brought to shore, and subsequently the police had brought him to the hospital. (Reprinted with permission from *DSM-V Casebook*.)

Patients with resolved transient amnesia (e.g., transient global amnesia) may have a superficially similar history retrospectively. They manifest failure of recall for matters or events that occurred during the discrete episode in question. Thorough clinical investigations of patients with amnestic disorder typically reveal a primary cerebral or systemic medical condition that is etiologically related to the genesis of the mental status abnormality. During an episode, patients with transient amnesia generally have a confused or bewildered demeanor and exhibit marked difficulty with new learning tasks. Episodes of psychogenic amnesia end abruptly, typically associated with an expressed awareness of having no memories for the time period of the amnestic or fugue state. In contrast, the retrograde memory defect of transient global amnesia gradually shortens as the patient recovers; when recovery is complete, the memory gap spans only the period of the episode.

**Course** Although the mode of onset is typically abrupt, data suggest that individuals with alcohol-induced amnestic disorder may develop deficits insidiously over many years as a result of repeated toxic and nutritional insults before the emergence of a final, dramatically impairing episode of illness apparently related to thiamine deficiency. Transient amnesia due to a cerebrovascular etiology may be recurrent, with episodes lasting from several hours to several days. Amnestic disorders due to head trauma, for example, may last variable amounts of time, with the greatest deficit apparent immediately after injury and improvement occurring during the ensuing 2 years (further improvement beyond 24 months has been noted, but less commonly). Full recovery may occur, although severe injuries are typically characterized by residual deficits. Disorders due to destruction of middle-temporal lobe structures, such as infarction, encephalitis, surgical ablation, or malnutrition in the context of alcohol dependence, may cause densely persisting impairments.

**Treatment** Whenever a primary systemic or cerebral disorder is causally tied to the amnestic syndrome, initial treatment (with thiamine, antiviral medication, aspirin) must be directed toward the underlying pathological process. Presently there are no known, definitively effective treatments for amnestic disorder that are specifically aimed at reversing apparent memory deficits. A variety of pharmacotherapeutic trials have been to no avail. Recently, centers for cognitive rehabilitation have been established whose rehabilitation-oriented therapeutic milieu is intended to promote recovery from brain injury, especially 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 patients who participate in such tasks as memory retraining. Persons with amnestic disturbances worthy of diagnosis experience major impediments in their social and vocational functioning. They may require supervised living situations to

ensure appropriate feeding and care.

**Other Cognitive Disorders** Disorders such as dementia and amnesia are specific categorical designations that are intended to define disease states. However, intellectual functioning can also be viewed from a dimensional perspective, ranging from optimal to grossly deficient. Dementia represents an abnormal decline from a previous level of attainment; mental retardation reflects the failure to develop adequate intellectual function.

Within this broad framework multiple domains of intellect are recognized that involve a wide variety of brain-related cognitive processes. The determination of normal and abnormal usually is made by comparing a person's performance on a variety of neuropsychological tests with predetermined normative standards. Ideally, the clinician would like lifelong (i.e., premorbid) serial cognitive testing to aid with diagnosis; occasionally, school, military, or vocational records provide an acceptable alternative. Usually one must compare a patient's results against published norms. Those norms may vary in quality, and the clinician should be aware whenever possible of factors such as the education, sex distribution, socioeconomic status, and age distribution of normative samples.

**Cognitive Disorder Not Otherwise Specified** DSM-IV includes a new diagnostic category, *cognitive disorder not otherwise specified,* to deal with patients whose clinical presentation does not conform to a diagnosis of delirium, dementia, or amnesia. The designation is useful for patients with mild deficits in cognitive functioning that result from conditions such as head trauma, chronic alcohol dependence, or HIV infection. In the recovering alcoholic, for example, or the patient with a significant but resolving posttraumatic amnesia, intellectual abnormalities may be detectable objectively and noted subjectively, although they may be only minimally impairing functionally. Those deficits may disappear over time or remain as subtle residua. HIV infection may cause a mild decline in cognition; current research has demonstrated such decrements repeatedly. Of note, the performance of many patients has remained within the normal range even as the test scores have decreased significantly. The diagnostic criteria for cognitive disorder not otherwise specified appear in Table 10-42.

This category is for disorders that are characterized by cognitive dysfunction presumed to be due to the direct physiological effects of a general medical condition that do not meet criteria for any of the specific deliriums, dementias, or amnestic disorders listed in this section and that are not better classified as delirium not otherwise specified, dementia not otherwise specified, or amnestic disorder not otherwise specified. For cognitive dysfunction due to a specific or unknown substance, the specific substance-related disorder not otherwise specified category should be used.
Examples include
1. Mild neurocognitive disorder: impairment in cognitive functioning as evidenced by neuropsychological testing or quantified clinical assessment accompanied by objective evidence of a systemic general medical condition of central nervous system dysfunction.
2. Postconcussional disorder: following a head trauma, impairment in memory or attention with associated symptoms.



**Table 10-42** DSM-IV Diagnostic Criteria for Cognitive Disorder Not Otherwise Specified

**Mild Neurocognitive Disorder** To define those conditions with greater specificity, the World Health Organization developed the ICD-10 diagnostic category of mild cognitive disorder (Table 10-43). A

similar DSM-IV construct (mild neurocognitive disorder) is included in an appendix as an example of cognitive disorder not otherwise specified. Table 10-44 lists the DSM-IV research criteria for mild neurocognitive disorder. To date, the interface between amnestic disorders or dementing disorders and mild neurocognitive disorder has not been defined reliably or validly.

**Table 10-43** ICD-10 Diagnostic Criteria for Other Mental Disorders Due to Brain Damage and Dysfunction and Due to Physical Disease

A. The presence of two (or more) of the following impairments in cognitive functioning, lasting most of the time for a period of at least 2 weeks (as reported by the individual or a reliable informant):
   (1) memory impairment (as identified by a reduced ability to learn or recall information)
   (2) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
   (3) disturbance in attention or speed of information processing
   (4) impairment in perceptual-motor abilities
   (5) impairment in language (e.g., comprehension, word finding)
B. There is objective evidence from physical examination or laboratory findings (including neuroimaging techniques) of a neurological or general medical condition that is judged to be etiologically related to the cognitive disturbance.
C. There is evidence from neuropsychological testing or quantified cognitive assessment of an abnormality or decline in performance.
D. The cognitive deficits cause marked distress or impairment in social, occupational, or other important areas of functioning and represent a decline from a previous level of functioning.
E. The cognitive disturbance does not meet criteria for a delirium, a dementia, or an amnestic disorder and is not better accounted for by another mental disorder (e.g., a substance-related disorder, major depressive disorder).



**Table 10-44** DSM-IV Research Criteria for Mild Neurocognitive Disorder

In addition to conditions such as HIV infection, head trauma, or alcohol dependence, mild cognitive decline with neuropsychological performance below the level of age-matched peers may be encountered as an early sign of a progressive degenerative disease. The use of cognitive disorder not otherwise specified as a diagnosis can serve to describe provisionally a patient who the physician suspects will develop a more malignant dementia of the Alzheimer's type and in whom a definitive diagnosis is premature owing to the relative mildness of the symptoms and an associated lack of clarity regarding clinical course. The label of not otherwise specified demands maximum clinical scrutiny and vigilance when employed in this fashion.

**Other Cognitive Conditions** Clinical investigators and geriatric psychiatrists have recently joined cognitive psychologists in studying aging-related cognitive decline involving such functions as spontaneous verbal memory, cognitive flexibility and abstracting ability, visuospatial processing, divided attention, speed of mental processing, and naming. Aging-related decrements in those functions do not relate to any specific or defined neuropathology, although they may reflect underlying neurobiological deterioration. Of note, objective documentation of individual decline in test performance may be impossible. Although experimental comparisons of groups of healthy older subjects with

comparably educated younger groups show consistent changes with aging, there are no data to suggest that the overall decline is a harbinger of disease.

Many persons with normal (i.e., normatively defined) aging-related intellectual decrements seek clinical evaluation for forgetfulness, especially out of fear that they may be developing Alzheimer's disease. Their complaints often include inability to recall names or words spontaneously, absent-mindedness, the need to use reminder lists, or subtle problems with concentration. Careful interviewing typically reveals mild anxiety about minor intellectual problems, the use of effective compensatory mental strategies, and intact personal and social functioning, with little evidence of definable interference from perceived cognitive inadequacies in their daily lives. The absence of significant functional decline, together with performance within the normative (i.e., based on similarly aged samples) range on neuropsychological testing, in the context of an unrevealing general medical evaluation points to aging-associated cognitive alterations.

Because of ample data on the phenomenon and clinicians' need to provide concerned patients with an understandable terminology to define their perceived difficulties, DSM-IV groups age-related cognitive decline among those conditions not attributable to a mental disorder that are a focus of attention or treatment. A variety of other common problems are included in that class, among them borderline intellectual functioning, academic problems, adult antisocial behavior, and marital problems.

Figure 10-16 presents schematically in a dimensional perspective the relations between increasing age and cognitive performance, depicting changes in the normative range, mild cognitive impairment, and dementia. The aging-related decline in normative performance underscores the difficulty of establishing an absolute standard of cognitive deficit that is indicative of impairment due to a categorical disease process. The figure also suggests that there will always be patients detected in the range of mild impairment. As long as there are few (or no) pathobiologically exact laboratory tests to determine with certainty specific cognitive impairment disorders, thoughtful clinical judgment will remain a central part of the diagnostic process.

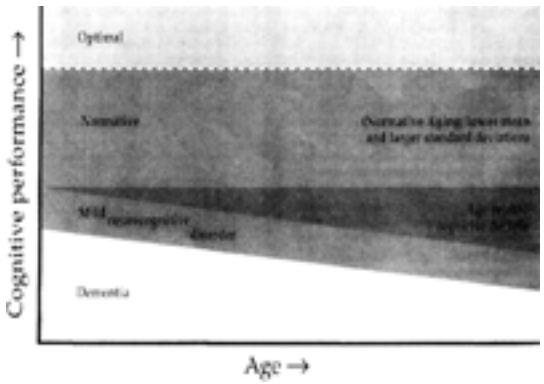



**FIGURE 10-16** Aging-associated changes in ranges of cognitive performance.

**Mental Disorders Due to a General Medical Condition** DSM-IV has taken a different approach to categorizing the mental disorders due to a general medical condition than did DSM-III-R. In DSM-III-R the disorders were classified under the broader category of organic mental disorders. In DSM-IV each

mental disorder due to a general medical condition is classified within the category that most resembles its symptoms (Table 10-45). For example, the diagnosis psychotic disorder due to a general medical condition is found in the DSM-IV section on schizophrenia and other psychotic disorders. The symptom-based organization of DSM-IV is meant to facilitate clinical decision making regarding the differential diagnosis of symptoms. For example, the clinician who is evaluating a patient with depression can refer to the DSM-IV section on mood disorders and find mood disorder due to a general medical condition as one of the diagnoses. That diagnosis should help to clarify the importance of considering the possibility of a mental disorder due to a general medical condition for almost all psychiatric presentations.

| DSM-IV Category | Mental Disorders due to a General Medical Condition |
|---|---|
| Delirium, dementia, amnestic, and other cognitive disorders | Delirium due to a general medical condition<br>Dementia due to other general medical conditions<br>Amnestic disorder due to a general medical condition |
| Schizophrenia and other psychotic disorders | Psychotic disorder due to a general medical condition |
| Mood disorders | Mood disorder due to a general medical condition |
| Anxiety disorders | Anxiety disorder due to a general medical condition |
| Sexual disorders | Sexual dysfunction due to a general medical condition |
| Sleep disorders | Sleep disorder due to a general medical condition |
| Mental disorders due to a general medical condition not elsewhere classified | Catatonic disorder due to a general medical condition<br>Personality change due to a general medical condition<br>Mental disorder not otherwise specified due to a general medical condition |

**Table 10-45** Mental Disorders Due to a General Medical Condition

**Mood Disorder Due to a General Medical Condition** Secondary mood syndromes are characterized by a prominent mood alteration that is thought to be the direct physiological effect of a specific medical illness or agent. These disorders are often difficult to define and have not been extensively researched; therefore, only limited information can be provided.

**Definition** The key feature is prominent, persistent, distressing, or functionally impairing depressed mood (anhedonia) or elevated, expansive, or irritable mood, judged to be caused by either an Axis III condition or by substance intoxication or withdrawal. Cognitive impairment is not the predominant clinical feature; otherwise, the mood disturbance would be viewed as part of delirium, dementia, or other cognitive deficit disorder. The diagnostician is asked to specify if the mood syndrome is manic, depressed, or mixed, and if criteria for a fully symptomatic major depressive or manic syndromic are fulfilled.

**History and Comparative Nosology** Mood disturbances secondary to medical conditions have long been described, but attention was rarely paid to the presence or absence of coexisting intellectual deficits. DSM-III introduced the term and the formal concept of organic affective syndrome, which required both mood alteration and two associated symptoms (as found in primary affective illnesses) to be present and thought due to specific medical etiologies. DSM-III-R eliminated the requirement for associated symptoms. DSM-IV marks the first explicit diagnostic criteria to denote whether or not the disturbance meets full major depressive or manic syndromic criteria. There has been much disagreement in the literature about primary depressive disorders and whether minor depressive disorders exist and how best to define them. Similar arguments might apply to lesser depressive syndromes of secondary origin. Terminology aside, there has been little research in the area of secondary mood disorders; what

data exist are hampered by differing (or absent) operationalization of what constitutes sufficient evidence for defining causality.

**Epidemiology** There are no clear data on which to base statements of incidence or prevalence of secondary mood disorders in any clinical or community population. It is clear that depressive symptoms and a wide array of systemic and primary cerebral conditions coexist to a far higher degree than can be explained by chance. Unfortunately, establishing a causal relation between depressive symptoms and a specific medical entity is difficult; therefore, the percentage of those coexisting symptoms that can be called secondary remains unknown. Further, many reported studies did not assess a range of syndromic criteria (i.e., major versus minor depression), and many simply quantified depressive symptoms by using rating scales without determining if the symptoms attained a threshold level of clinical significance. One noteworthy point is that depression in the medically ill appears to be equally prevalent by sex, or possibly slightly higher in men than in women. This disparity, when compared with the preponderance of females with primary depressive disorders, is often cited as an indicator of the importance of viewing secondary mood disturbances separately.

Rates of mood disorder in the medically ill have been carefully described in several neurological diseases. For example, at least one research group has documented high rates of criteria-defined major and minor depressive syndromes in patients shortly after cerebrovascular accidents. Correlation of stroke lesion location and size with presence (and possibly with type) of depressive syndrome suggests the role of direct disruption of brain physiology as a causal mechanism. Also, the presence or severity of depression does not correlate highly with physical impairment due to hemiparesis, for example, and may be higher than rates found in patients with similar levels of overall disability due to nonneurological conditions, suggesting that depression in neurological patients is not simply a psychological reaction to illness and disability. Similarly, less extensive descriptions of increased rates of depressive symptoms and syndromes have been reported for populations with Parkinson's disease, Huntington's disease, HIV infection (with presumed direct CNS involvement), and multiple sclerosis.

Determination of the secondary or symptomatic nature of these mood syndromes is problematic and is further complicated by the fact that at least some of the patients with these neurological illnesses had substantial cognitive impairment. Although DSM-IV attempts to address these issues directly, uncertainties remain. For example, if a patient with Huntington's disease has dementia and a depressive syndrome, the clinician might choose the diagnosis of dementia due to Huntington's disease with depressed mood. However, early in the disease process a syndromically depressed Huntington's patient with few cognitive impairments would warrant a diagnosis of mood disorder due to Huntington's disease with major depressive episode. As the intellectual impairment progresses, does the clinician abandon one diagnosis for another or add a second Axis I diagnosis of dementia? Such borderline situations are expected to generate uncertainty, which can be ameliorated by careful documentation of one's clinical reasoning.

Secondary mania appears to be much less prevalent in most neurological illnesses, with the exceptions of multiple sclerosis and possibly Huntington's disease. Case reports abound of putative secondary

mania due to a variety of other causes, but the prevalence is not known. Finally, patients with secondary mood syndromes may have increased rates of prior mood disorders and higher rates of family history of mood disorder. Therefore, secondary syndromes may reflect an interaction between a precipitating agent or illness and the patient's diathesis toward mood pathology.

**Etiology** The list of potential causes for both depressive and manic syndromes is long. Table 10-46 lists some of the causes most commonly considered.

**Table 10-46** Causes of Secondary Mood Disorders

**Diagnosis and Clinical Features** The depressive or manic symptoms found in secondary mood disorders are phenomenologically similar to those found in primary (idiopathic) mood disorders. It is not known if certain symptoms occur more commonly in the secondary disorders; presumably the prevalence may vary depending on the specific etiology of the secondary disorder. For example, anxiety has been described as prominent in major depressive syndromes seen in patients with Parkinson's disease; however, no studies have compared depressed patients with Parkinson's disease with similarly aged patients experiencing idiopathic major depressive disorder.

Associated clinical phenomena may include other manifestations of the cause of the secondary mood disorder, such as soft neurological signs or contributing cognitive impairment; indeed, those findings are used to support the assessment of the mood symptoms as secondary in origin. There are no specific tests to confirm the diagnosis of a secondary mood disorder. In addition, little is known about how neurobiological abnormalities seen in idiopathic mood disorders differ from secondary syndromes. Moreover, despite recent interest in secondary mood disorders, there is still little definitive understanding of the neuroanatomical substrate of those disorders. Physical (including neurological) examination and specific laboratory tests or procedures may be crucial to establishing the presence of the primary disease state.

**Differential Diagnosis** There are two broad domains of differential diagnosis to consider when establishing the presence of a secondary mood disorder. The first is phenomenological: Does the patient have clinically significant manic or depressive symptoms in the absence of evidence of a predominant cognitive deficit? That assessment requires attention to symptoms and function in the history and mental status examination. As part of the process, the clinician is also establishing whether there is a clearly defined mood syndrome sufficient to warrant an empirical treatment trial with antidepressant

medications.

The second domain is etiological: Does the patient have an Axis III condition or a state of substance intoxication or withdrawal that is causing the mood disturbance? Establishing the presence of the relevant condition depends on standard psychiatric and medical-neurological assessments; establishing the causal relation to the mood disorder may be difficult.

**Course and Prognosis** Although the literature on the course of clearly defined secondary mood disorders is scant, substantial work has demonstrated that all depressive conditions that are comorbid with general medical illnesses or substance-related disorders have poorer prognoses than those that have no demonstrated associations, whether measured by means of symptomatic expression, functional disability, or mortality. It is therefore likely that secondary depressive illness is most often a chronic disease that is sometimes characterized by periods of remission followed by recurrences and sometimes by continuous illness. The prognosis varies, depending on the etiological disease state; depression secondary to a readily treatable disease (e.g., hypothyroidism) has a better outcome than depression associated with a terminal, essentially untreatable condition (e.g., metastatic pancreatic carcinoma). Little is known about the relation of specific depressive syndromes to outcome even within a specific etiological group. For example, there have been attempts to distinguish outcome in poststroke patients based on the presence of minor or major depressive syndromes; this work has had little replication by other investigator groups and the results may not generalize to depression secondary to other conditions. There is even less information available on the course of secondary mania, although many case reports suggest it is chronic and refractory to treatment.

**Treatment** Treatment response has received limited study. Standard antidepressant medications (e.g., tricyclic antidepressants, MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), and ECT are effective in many depressed patients with medical and neurological illnesses or substance use disorders. However, the utility of studies of antidepressant drugs has been limited by the scant clinical definition of study patients in many publications; a designation of secondary mood disorder, with depressive features, provides little information on specific target symptoms and their response. The efficacy of newer somatic agents (e.g., SSRIs, bupropion [Wellbutrin]) and of newer psychotherapeutic approaches has received little systematic study. A comparison of response to specific treatment modalities in syndromically similar primary and secondary mood disorders has not been done. However, the comorbid pathology found in secondary syndromes may limit treatment trials, either because of contraindications or because of increased susceptibility to adverse effects.

Given the severely limited data, the clinician treating a patient with a secondary mood disorder must rely on the following general guidelines. The underlying causes should be treated as effectively as possible. Persisting manic or major depressive syndromes are likely to require somatic therapies; standard treatment approaches as used for the corresponding primary mood disorder should be employed, although the risk of toxic effects may require more gradual dosage increases. At a minimum, psychotherapy should focus on psychoeducational issues (in particular, the concept of a secondary behavioral disturbance may be new or difficult for many patients and families) and support. More

specific intrapsychic, interpersonal, and family issues are addressed as indicated. Approaches to subsyndromal secondary mood disorders are even less well established, but clinically significant disturbances warrant empirical trials of the same treatments used in fully syndromic patients.

**Psychotic Disorder Due to a General Medical Condition** *Psychosis* has been a term of inconsistent definition, used in recent years to refer exclusively to symptoms of a striking nature, such as hallucinations and delusions, but in the past to severe affective syndrome (e.g., psychotic versus neurotic depression); to cognitive symptoms, such as confusion, disorientation, or altered memory (such as Korsakoff's psychosis); or as a means of describing the severity of any psychiatric symptom ("of psychotic proportions"). DSM-III-R in its appended glossary defined psychosis as "gross impairment in reality testing and the creation of a new reality." Hallucinations, delusions, bizarre behavior, and incoherent speech were considered direct evidence of psychosis. Psychotic symptoms have been recognized as nonspecific, as they can be seen in any of the major psychiatric illnesses, such as dementia, schizophrenia, or bipolar I disorder, as well as in many systemic medical or cerebral disorders.

**Definition** In order to establish the diagnosis of psychotic disorder due to a general medical condition the clinician first must exclude syndromes in which psychotic symptoms may be present in association with cognitive impairment (e.g., delirium and dementia of the Alzheimer's type) but not the defining feature, and the clinician must determine with confidence the causal link. In turn, secondary psychotic disorders must be excluded before a diagnosis of a primary (idiopathic) psychotic disorder is entertained.

**History** Psychotic symptoms, including delusions, hallucinations, incoherent speech or formal thought disorder, and bizarre behavior, have been recognized for centuries. In medical prehistory they were perceived in a theological light as evidence of demonic possession or punishment for a moral failing. In the eighteenth century, at the threshold of the modern brain disease model, psychosis was sometimes attributed to a bodily dysfunction, either systemic or related specifically to the CNS. However, tension has persisted among clinicians since the 1800s as to whether psychotic symptoms are the manifestations of a dysfunctional brain or are volitional or psychological reactions to life circumstances. Reports of secondary psychosis have abounded for centuries and have contributed to an understanding of those behaviors as specific symptoms of brain disease. Many descriptions, however, have had limited use because of vagaries in the definition of psychosis and the lack of any uniform means for establishing a correlation between psychotic symptoms and the associated systemic or cerebral medical condition under study.

Recently, three types of investigations have emerged for the study of secondary syndromes, including secondary psychosis. One type of study compares psychopathological symptoms in patient groups with and without known primary medical conditions. This comparison has been done strictly on a retrospective basis for secondary psychosis, with only one available prospective study of secondary delusional disorders. Another type of investigation has examined patient groups with known CNS disease, such as cerebrovascular disorder or Huntington's disease, with a careful description of any associated psychopathology. The third investigative track has selected patients with known psychopathology, such as hallucinations in schizophrenia, and sought evidence to correlate symptoms with CNS dysfunction using a variety of measures (e.g., neuroimaging of the temporal lobe). The

secondary psychotic disorders are a window through which insights into the neurobiological basis for psychotic processes may be obtained.

**Comparative Nosology** Secondary psychotic syndromes were categorized in DSM-II as psychoses associated with organic brain syndromes. The syndromes included in that category were the dementias, deliria, and psychoses associated with other cerebral and systemic conditions. Entry into the category depended on cognitive symptoms, such as disturbances of orientation, memory, judgment, and lability of affect. The term “psychosis” continued to be used for the sake of historic continuity, with the acknowledgment that “many patients for whom these diagnoses are clinically justified are not in fact psychotic.” DSM-III improved on the nosology by establishing the general rubric of organic brain syndromes, with six specific syndromes, including organic hallucinosis and organic delusional syndrome. In DSM-IV, psychotic disorder due to a general medical condition (with its available subtypes) has been moved out of the organic group to the phenomenological cluster to which it is related. This shift underscores the need for differential diagnosis, the clinical importance of defining etiology whenever possible, and the idea that primary psychopathology is idiopathic—that is, without known cause.

**Epidemiology** The incidence and prevalence of secondary psychotic disorders in the general population are unknown. The prevalence of psychotic symptoms is increased in selected clinical populations, such as nursing home residents with dementia of the Alzheimer's type, but it is unclear how to extrapolate these findings to other patient groups.

**Etiology** Virtually any cerebral or systemic disease that affects brain function can produce psychotic symptoms. Table 10-27 lists examples within each of the broad categories of diseases that can produce dementia; each of those diseases is also capable of producing psychotic symptoms, both in the presence and in the absence of cognitive impairment. Degenerative disorders, such as Alzheimer's disease or Huntington's disease, may present initially with new-onset psychosis, with minimal evidence of cognitive impairment at the earliest stages.

**Diagnosis and Clinical Features** To establish the diagnosis of a secondary psychotic syndrome (see Table 13.3-13). The clinician first determines that the patient is not delirious, as evidenced by a stable level of consciousness. A careful mental status assessment is conducted to exclude significant cognitive impairments, such as those encountered in dementia or amnestic disorder. The next step is to search for systemic or cerebral diseases that might be causally related to the psychosis. Psychotic symptomatology per se is not helpful in distinguishing a secondary from a primary (idiopathic) cause.

Comparative studies have not demonstrated any distinguishing phenomenological features in secondary psychosis or any difference in frequency or severity of the psychosis when compared to idiopathic psychosis. Olfactory and auditory hallucinations, although claimed anecdotally to suggest a secondary or symptomatic etiology, have proved unreliable. Some studies have suggested that exclusively positive psychotic symptoms, in the absence of negative symptoms and personality change, reflect a secondary cause; this suggestion has not been tested prospectively. Age at onset is a factor that should alert

clinicians to the possible emergence of a secondary psychotic disorder, reflecting both the age-related increased prevalence of diseases affecting brain function and the natural history of primary psychotic syndromes, with their markedly diminished incidence after ages 40 to 45 years.

All patients who present with the new onset of psychotic symptoms should undergo a thorough clinical evaluation emphasizing personal medical history, family medical history, and medical review of systems. A systematic physical and neurological examination should be performed. (The examiner should bear in mind, however, that nonlocalizing, soft neurological signs and a variety of dyskinesias can be present in idiopathic schizophrenia, even in the drug-naïve patient.) A neuroimaging evaluation with MRI for any new-onset psychosis, irrespective of patient age, is recommended. The detection of a systemic or cerebral abnormality does not automatically lead to the determination of secondary psychosis; establishing a secondary status requires thoughtful clinical reasoning.

**Differential Diagnosis** The differential diagnosis involves first establishing that the symptoms and signs encountered are in fact psychotic, according to the more specific modern definition. Confabulation may be mistaken for delusions. *Confabulation* is the spontaneous or prompted production of inconsistent and fabricated statements, often in response to questions or environmental stimuli. Although memory impairment is present in those who confabulate, the more salient cognitive deficit involves an inability to suppress or self-analyze the automatic fabrications and responses. Confabulation differs from delusions in that the fabricated beliefs are quite transient and varying. A behavioral response to the confabulated belief is usually absent. The presence of confabulation is also suggestive of brain disease, often involving the anterior temporal lobe (memory impairment) and the frontal lobes (loss of self-analysis). Perceptual disturbances that result in illusions or other misinterpretations of environmental stimuli must be distinguished from hallucinations, which are experienced as true perceptual experiences but without an actual stimulus.

*Agnosias*, or deficit syndromes, such as *prosopagnosia*, *topographic agnosia*, or *phonagnosia* (inability to recognize familiar faces, places, or sounds, respectively), can occur in the context of intact peripheral perception and can be mistaken for delusional beliefs as well as hallucinations. It is important to distinguish these deficit syndromes and to recognize that they point to parietal lobe dysfunctions that are not associated with other psychotic symptoms.

The phenomenology or type of psychotic symptom does not help distinguish idiopathic from secondary etiologies. However, once the suspicion of a secondary etiology has arisen, the specific psychotic presentation may suggest a particular brain region or direction for further investigation. Table 10-47 lists a number of specific psychotic symptoms that have been consistently associated with disease in particular brain regions. *First-rank symptoms*, originally described by Kurt Schneider as pathognomonic symptoms of schizophrenia, are now accepted as nonspecific psychotic symptoms occurring in all psychotic disorders. Although nonspecific for diagnosis, they have been associated with abnormalities in the left temporal lobe. Complex delusions have been associated with lesions in subcortical regions. Simple persecutory ideas are more common than complex or systematized delusions in patients with significant cognitive deficits. Patients apparently require a variety of intact intellectual abilities (and

presumably underlying brain substrate) in order to produce psychotic symptoms of greater complexity. *Anton's syndrome* refers to denial of blindness, classically described in patients with acquired cortical blindness arising from bilateral occipital cortex damage. More recently, it has been described in patients with peripheral optic neuropathy, suggesting that the syndrome may be a variant of the other denial-of-deficit syndromes, such as anosognosia. *Misidentification syndromes* have been described primarily in idiopathic psychotic disorders, although recent studies have pointed to nondominant parietal and frontal lesions as the basis for many. One recent neuropsychological theory proposes that the right hemisphere plays a role in the appreciation of the individuality or uniqueness of people, places, and objects and that lesions in the right hemisphere can result in delusions of misidentification.

| Symptoms | Site | Laterality |
|---|---|---|
| First-rank symptoms<br>Thoughts spoken aloud<br>Voices commenting<br>Third-person voices arguing<br>Made actions<br>Made feelings<br>Thought withdrawal<br>Thought diffusion<br>Delusional perception | Temporal lobe | Dominant hemisphere |
| Complex delusions | Subcortical or limbic | |
| Anton syndrome | Occipital lobe, optic tract | Bilateral |
| Anosognosia | Parietal lobe | Nondominant hemisphere |
| Misidentification syndromes<br>Capgras syndrome<br>Reduplicative paramnesia<br>Fregoli syndrome<br>Intermetamorphosis syndrome | Parietal, temporal, frontal lobes | Nondominant hemisphere, bilateral |

**Table 10-47** Psychotic Symptoms Associated With Abnormality of Specific Brain Regions

**Course and Prognosis** The course and prognosis of secondary psychotic syndromes depend on their etiology. Vivid psychotic symptoms arising from head trauma may improve dramatically during recovery. Delusions associated with degenerative diseases may diminish as the disease worsens, for the capacity to generate those more complex cognitions is gradually lost. Some secondary psychotic disorders improve with treatment of the underlying disorder, such as the interictal psychosis of epilepsy, which often improves with the pharmacological or surgical control of seizures. Psychotic disorders secondary to infectious disease may not improve, despite eradication of the infectious organism, because of irreversible tissue damage sustained during the acute infection.

**Treatment** The principles of treatment for a secondary psychotic disorder are similar to those for any secondary neuropsychiatric disorder, namely, rapid identification of the etiological agent and treatment of the underlying cause. Antipsychotics medications afford empirical symptomatic treatment for the psychotic symptoms, although secondary psychotic disorders often prove more refractory than idiopathic disorders to such treatment. Patients with primary systemic or cerebral diseases frequently are more vulnerable to the untoward adverse effects of antipsychotic drugs. To date, there has been insufficient use of serotonin-dopamine antagonists, such as clozapine (Clozaril), to judge their utility with these conditions.

**Anxiety Disorder Due to a General Medical Condition** Secondary anxiety syndromes are characterized by prominent anxiety symptoms that are thought to be the direct physiological effect of a specific physical illness or agent. Those disorders have received even less careful scrutiny than secondary mood disorders; therefore, the qualifications made in the section above apply equally or more

so to the following discussion.

**Definition** The key feature of anxiety disorder due to a general medical condition is the presence of prominent anxiety symptoms, which may include generalized anxiety, panic attacks, obsessions, compulsions, or phobias and which are judged to be caused by either an Axis III condition or by substance intoxication or withdrawal. In addition, the anxiety symptoms are not thought to be better explained by another mental disorder (e.g., the anxiety that can be seen in delirium or adjustment disorder with anxious mood). The diagnostician is asked to specify if the anxiety syndrome includes generalized anxiety, panic attacks, obsessive-compulsive symptoms, or phobias.

**History and Comparative Nosology** For centuries clinicians have described anxiety symptoms as prominent features in a variety of conditions; for most of the twentieth century many of those descriptions focused on patients with endocrinopathies, neurological illnesses, mitral valve prolapse, and substance-related states. The formal concept of any organic mental disorder other than cognitive disorders was introduced by DSM-III; however, organic anxiety disorder was not presented as a distinct entity until DSM-III-R. DSM-III-R limited the diagnosis to either generalized anxiety or panic attacks; DSM-IV broadens the possible related phenomena to include obsessions and compulsions.

Secondary anxiety syndromes have received little study. There are numerous descriptions of anxiety symptoms associated with medical illness or substance-related states, but the operationalization of "secondariness" is generally absent. Further, most studies have included patients with generalized anxiety or panic symptoms; reports of secondary obsessive-compulsive phenomena are few.

**Epidemiology** The prevalence of anxiety symptoms is high in general medical patients and in patients with many of the specific medical illnesses that are putative potential causes for secondary anxiety syndromes. However, the incidence and prevalence of secondary anxiety disorders, obtained from well-operationalized criteria for syndromic and etiological diagnosis, are not known. Similarly, rates of prior anxiety disturbances or of a family history for anxiety disorders are not known.

**Etiology** The list of potential causes for anxiety syndromes is long, with nearly complete overlap with the potential causes for mood syndromes. Causes most commonly described in anxiety syndromes include substance-related states (intoxication with caffeine, cocaine, amphetamines, and other sympathomimetic agents; withdrawal from nicotine, sedative-hypnotics, and alcohol), endocrinopathies (especially pheochromocytoma, hyperthyroidism, hypercortisolemic states, and hyperparathyroidism), metabolic derangements (e.g., hypoxemia, hypercalcemia, and hypoglycemia), and neurological disorders (including vascular, trauma, and degenerative). Many of these conditions are either inherently transient or easily remediable. Whether that reflects the pathophysiology of secondary anxiety or is an artifact of reporting (e.g., anxiety with subacute onset and complete resolution after removal of a pheochromocytoma is more likely to be reported as an example of anxiety due to a medical illness than is chronic anxiety in the context of chronic obstructive pulmonary disease) is not known. Much attention has been paid to the association of panic attacks and mitral valve prolapse. The nature of that association is unknown, and therefore the diagnosis of panic attacks secondary to mitral valve prolapse currently is

premature. Interestingly, several recent reports have sought to tie obsessive-compulsive symptoms to the development of pathology in the basal ganglia.

**Diagnosis and Clinical Features** The symptoms of secondary anxiety disorders are by definition phenomenologically similar to those found in the corresponding primary anxiety disorder (e.g., panic attacks and obsessions). It is not known if certain symptoms are seen more commonly in the secondary variety; presumably the rate of co-occurrence may vary, depending on the specific etiology of the secondary disorder. As with all secondary syndromes, associated clinical phenomena may include other manifestations of the cause of the secondary anxiety disorder, such as soft neurological signs or subtle cognitive impairment (which may have been used to support the assessment of the anxiety symptoms as being secondary in origin).

There are no specific tests to confirm the diagnosis of secondary anxiety disorder, and little is known about how neurobiological abnormalities seen in primary anxiety disorders differ in secondary syndromes. Physical (including neurological) examination and specific laboratory tests or procedures may be necessary to establish the presence of the etiological disease state.

**Differential Diagnosis** As for other secondary disorders, two broad domains of differential diagnosis must be considered to establish the presence of a secondary anxiety disorder. The first is phenomenological: does the patient have clinically significant anxiety, panic attacks, obsessions, or compulsions, along with an absence of evidence for another primary or secondary psychiatric syndrome? The second is etiological: does the patient have an Axis III condition, or a state of substance intoxication or withdrawal, that is causing the phenomenology? As always, establishing the causal relationship may be difficult.

**Course and Prognosis** Little information is available on the course of secondary anxiety disorders. The outcome presumably depends on the specific etiology; thus, anxiety due to hyperthyroidism may well remit with treatment of the hyperthyroid state whereas anxiety due to cardiomyopathy with a low-output state may run a more chronic course.

**Treatment** Well-designed treatment studies of carefully described patients with secondary anxiety disorders are lacking. Aside from treating the underlying causes, clinicians have found benzodiazepines to be helpful in decreasing anxiety symptoms; supportive psychotherapy (including psychoeducational issues focusing on the diagnosis and prognosis) may also be useful. The efficacy of other, more specific therapies in secondary syndromes (e.g., antidepressant medications for panic attacks, SSRIs for obsessive-compulsive symptoms, behavior therapy for simple phobias) is unknown.

**Sleep Disorder Due to a General Medical Condition** Sleep disorders can result from a diversity of causes, among them stressful life circumstances, crossing time zones, pulmonary or laryngeal structural abnormalities, systemic diseases (e.g., renal failure), or primary cerebral pathology. However, many sleep disorders, such as narcolepsy, sleep terrors, and enuresis, are idiopathic and occur without known systemic or central abnormalities. The epidemiology of secondary sleep disorders has not been studied

systematically.

**Definition and Diagnosis** Sleep disorders can manifest in four ways: by an excess of sleep (*hypersomnia*), by a deficiency of sleep (*insomnia*), by abnormal behavior or activity during sleep (*parasomnia*), and by a disturbance in the timing of sleep (*circadian rhythm sleep disorders*). Primary sleep disorders occur unrelated to any other medical or psychiatric illness. The DSM-IV nosology is deliberately simple and nondetailed. The patient is assigned to broad categories based on presenting symptoms and the etiological consideration of primary versus secondary disorder. The *International Classification of Sleep Disorder* is a more comprehensive and detailed nosology that requires the usage of polysomnography for many of the diagnoses.

**Etiology and Differential Diagnosis** Table 10-48 lists a number of conditions in which a disturbance of sleep has been frequently and characteristically described, allowing conditions to be designated as causes of secondary sleep disorder. *Parkinsonism*, related to either idiopathic Parkinson's disease, medications, or head trauma, frequently results in a secondary sleep disorder. As many as 75 percent of patients with Parkinson's disease complain of sleep disturbance, usually frequent awakenings during sleep. The difficulty maintaining sleep can have a number of causes. Sleep is fragmented owing to the brain degeneration that disrupts the neurophysiological and neurochemical pathways of sleep. In addition, the symptoms of Parkinson's disease can disrupt sleep. Although tremor is diminished during sleep, muscular rigidity is increased and can prevent the patient from turning or finding a comfortable position, resulting in arousal and awakening. Medications used to treat Parkinson's disease can disrupt sleep. Levodopa preparations frequently cause disruptive dreams and nightmares and may also increase nocturnal myoclonus, repetitive, brief leg jerks that awaken the patient and fragment sleep. Levodopa can be stimulating and may prevent the initiation of sleep if taken close to bedtime. Dementia due to degenerative disease can impinge on sleep in a manner similar to parkinsonism, with the degeneration of pathways vital for normal sleep. *Sundowning*, the emergence of severely disruptive behavior, such as agitation and paranoia, at night, associated with the inability to maintain sleep, is a major management issue in the home care of patients with dementia. The pathophysiology is unknown at present, although some have speculated that sundowning is a nocturnal delirium secondary to degeneration of the suprachiasmatic nucleus. Alternatively, sundowning is viewed as a disruption of circadian rhythms, rapid eye movement (REM) parasomnias, or simply postawakening confusion during which the patient with dementia is unable to distinguish between dreams and current reality. Dementia of the Alzheimer's type is accompanied by an exaggeration of the sleep changes associated with normal aging, with a decrease in total sleep time as well as in slow wave and REM sleep. The sleep disturbances worsen as the disease progresses.

**Table 10-48** Medical Conditions Commonly Associated With a Secondary Sleep Disorder

| Condition | Sleep Symptoms |
|---|---|
| Parkinsonism | Frequent awakenings, disturbance of circadian rhythms |
| Dementia | Sundowning, frequent awakenings |
| Epilepsy | Difficulty initiating sleep, frequent awakenings, parasomnias |
| Cerebrovascular disease | Difficulty initiating sleep, frequent awakenings |
| Huntington's disease | Frequent awakening |
| Kleine-Levin syndrome | Hypersomnia |
| Uremia | Restless legs, nocturnal myoclonus |

Epilepsy can be a true sleep disorder. Most seizure disorders are activated by sleep or arousal from sleep. Both local and generalized epilepsy can occur during sleep, resulting in difficulties maintaining sleep. Seizures may manifest as parasomnias, such as night terrors, sleepwalking, or head banging, although most parasomnias are not related to epilepsy.

Cerebrovascular disorders can impinge on the initiation and maintenance of sleep. No specific lesions have been consistently correlated with a particular sleep disturbance, although brainstem lesions in general are apt to disrupt sleep architecture.

In *Huntington's disease* patients experience frequent awakenings and decreased total sleep time, a pattern common to many subcortical dementia syndromes. With the progression of the disease the movement disorder may manifest during sleep, further disrupting sleep.

Chronic renal failure, anemia, and diabetes mellitus can cause nocturnal myoclonus and the *restless legs syndrome*. The latter is characterized by the experience of deep pains in the lower calf, prompting the patient to keep the legs in constant motion and impinging severely on the ability to initiate sleep.

*Kleine-Levin syndrome* is a rare disorder characterized by hypersomnia, compulsive eating, sexual disinhibition, personality change, and psychosis. There is a 3 to 1 male-to-female predominance, with onset of symptoms typically occurring in adolescence. Hypersomnia is marked and is the most consistent feature. Compulsive eating and sexual disinhibition, such as public masturbation or propositioning of strangers, complete the syndrome. Incomplete or atypical variants are more common than the full syndrome. Irritability is frequent, and hallucinations or affective symptoms may be present. Symptoms last hours to weeks and are cyclical, with a full return to baseline on many occasions. Symptoms recur in a varying frequency of 1 to several months. The syndrome can be preceded by flulike symptoms or head trauma, although the precise etiology and pathophysiology are unknown. Presumably, there is hypothalamic system dysfunction with the manifest disturbances in sleep, eating, and sexual behavior. In most patients the episodes decrease in frequency and eventually disappear entirely.

**Treatment** The diagnosis of a secondary sleep disorder hinges on the identification of an active disease process known to exert the observed effect on sleep. Treatment first addresses the underlying neurological or medical disease. Symptomatic treatments focus on behavior modifications, such as

improvement of sleep hygiene. Pharmacological options may also be used, such as benzodiazepines for restless legs syndrome or nocturnal myoclonus, stimulants for hypersomnia, and tricyclic antidepressant medications for manipulation of REM sleep.

**Sexual Dysfunction Due to a General Medical Condition** Specific syndromes characterized by sexual dysfunction thought to be physiologically caused by a general medical condition are female or male hypoactive sexual desire disorder, male erectile disorder, dyspareunia, and other male or female sexual dysfunction.

**History and Comparative Nosology** Numerous medical conditions, medications, and drugs of abuse can affect sexual desire and performance. However, despite the attention psychiatry has paid to presumed psychologically mediated sexual dysfunction, the role of physiological diseases was downplayed in earlier psychiatric diagnostic systems. DSM-III listed only functional sexual dysfunctions. DSM-III-R allowed sexual dysfunctions to be classified as psychogenic only or as due to both biogenic and psychogenic causes, but required purely biogenic syndromes to be coded on Axis III. The inclusion of secondary sexual disorders as Axis I diagnoses in DSM-IV is consistent with that edition's inclusive approach to behavioral syndromes.

**Epidemiology** Although surveys have repeatedly demonstrated a high prevalence of sexual dysfunctions in the general population, valid data on secondary dysfunctions are lacking. Similarly, certain medications may be associated with specific rates of sexual symptoms, but the percentage of patients with truly secondary syndromes is not known.

**Etiology** Potential causes of sexual dysfunctions are listed in Table 10-49. The type of sexual dysfunction is affected by the etiology, but specificity is rare; that is, a given etiology may manifest as one (or more than one) of several syndromes. General categories include medications and drugs of abuse, local disease processes that affect the primary or secondary sexual organs, and systemic illnesses that affect sexual organs via neurological, vascular, or endocrinological routes.


**Medications**
Cardiac drugs, antihypertensives (e.g., reserpine, β-adrenergic recep-
tor antagonists clonidine, α-methyldopa, diuretics)
$H_2$-receptor blockers
Carbonic anhydrase inhibitors
Anticholinergics
Anticonvulsants (e.g., carbamazepine, phenytoin, primidone)
Antipsychotics
Antidepressants (e.g., tricyclics, MAO oxidase inhibitors, trazodone,
SSRIs)
Sedative-hypnotics
**Substances of abuse**
Alcohol
Opioids
Stimulants
Cannabis
Sedative-hypnotics
**Local disease processes that affect primary or secondary sexual organs**
Congenital anomalies or malformations
Trauma
Tumor
Infection
Postsurgical or postirradiation local neurological and vascular pa-
thology
**Systemic disease processes**
Neurological
Central nervous system (e.g., stroke, multiple sclerosis)
Peripheral nervous system (e.g., peripheral neuropathy)
Vascular
Atherosclerosis, vasculitis (as examples)
Endocrine
Diabetes mellitus, alterations in function of thyroid, adrenal cortex,
gonadotropins, gonadal hormones (as examples)

**Table 10-49** Causes of Secondary Sexual Dysfunctions

**Diagnosis and Clinical Features** The clinical features of the sexual dysfunction resemble those of the various primary dysfunctions. There may be additional findings due to the underlying disease process.

For example, in male erectile disorder due to diabetic autonomic neuropathy, the patient may have symptoms of bowel and bladder autonomic dysfunction as well as evidence of diabetes mellitus itself.

**Differential Diagnosis** Phenomenology determines the syndromic diagnosis (e.g., erectile dysfunction versus orgasmic disorder). Medical history, physical examination, and relevant laboratory testing are required to demonstrate the presence of physical conditions that are potentially etiological for the sexual dysfunction. However, presence alone does not establish an etiological link. Clinical judgment is necessary and is based on temporal association, assessment of potentially contributory psychosocial factors (or more gross psychopathology), and other factors; the determination of secondary status is often difficult. One exception to that difficulty is male erectile dysfunction. Patients with secondary erectile dysfunction are unable to sustain erections under any circumstances whereas those with primary (i.e., psychogenic) disorders may give a history of variable erectile ability, depending on environment, partner, or other circumstances. If in doubt, a nocturnal penile tumescence study may be helpful because only males with secondary erectile dysfunction will fail to demonstrate tumescence during sleep.

**Course and Prognosis** The course and prognosis of secondary sexual dysfunctions vary widely, depending on the etiology. Drug-induced syndromes generally remit with discontinuation (or dosage reduction) of the offending agent. Endocrine-based dysfunctions also generally improve with restoration of normal physiology. By contrast, dysfunctions due to neurological disease may run protracted, even progressive, courses.

**Treatment** The treatment approach varies widely, depending on the etiology. When reversal of the underlying cause is not possible, supportive and behaviorally oriented psychotherapy with the patient (and perhaps the partner) may minimize distress and increase sexual satisfaction (e.g., example, by developing sexual interactions that are not limited by the specific dysfunction). Support groups for people with specific types of dysfunction are available. Other symptom-based treatments may be used in certain conditions; for example, sildenfanil (Viagra) administration or surgical implantation of a penile prosthesis may be used in the treatment of male erectile dysfunction.

**Mental Disorders Due to a General Medical Condition Not Elsewhere Classified** DSM-IV has three additional diagnostic categories for clinical presentations of mental disorders due to a general medical condition that do not meet the diagnostic criteria for specific diagnoses. The first of the diagnoses is catatonic disorder due to a general medical condition (Table 10-50). The second diagnosis is personality change due to a general medical condition. The third diagnosis is mental disorder not otherwise specified due to a general medical condition (Table 10-51).

**Table 10-50** DSM-IV Diagnostic Criteria for Catatonic Disorder Due to a General Medical Condition

A. The presence of catatonia as manifested by motoric immobility, excessive motor activity that is apparently purposeless and not influenced by external stimuli, extreme negativism or mutism, peculiarities of voluntary movement, or echolalia or echopraxia.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.
C. The disturbance is not better accounted for by another mental disorder (e.g., a manic episode).
D. The disturbance does not occur exclusively during the course of a delirium.

**Coding note:** Include the name of the general medical condition on Axis I, e.g., catatonic disorder due to hepatic encephalopathy; also code the general medical condition on Axis III.



This residual category should be used for situations in which it has been established that the disturbance is caused by the direct physiological effects of a general medical condition, but the criteria are not met for a specific mental disorder due to a general medical condition (e.g., dissociative symptoms due to a complex partial seizure).

**Coding note:** Include the name of the general medical condition on Axis I, e.g., mental disorder not otherwise specified due to HIV disease; also code the general medical condition on Axis III.



**Table 10-51** DSM-IV Mental Disorder Not Otherwise Specified Due to a General Medical Condition

**Personality Change Due to a General Medical Condition** Personality refers to the constellation of enduring traits and behavioral style that essentially defines the person. Personality develops through adolescence and achieves a degree of stability in early adulthood. Both biological disposition as well as environmental factors influence the development of personality. In adults, behavioral style can be described in terms of interests, activities, pleasures, social relations, predominant mood and temperament, standards, usual outlook on life, range of coping mechanisms, and so forth. There is a robust theoretical and clinical literature delineating specific traits, such as self-consciousness, impulsivity, gregariousness, excitement-seeking, openness, and so forth, along dimensions or continua. Standardized measures are available to determine where along the spectrum for each trait a particular patient lies. This provides a personality profile that can be considered relative to standardized norms. The process is quite similar to the dimensional perspective used to assess intelligence and the determination of an I.Q.

The past concept of organic personality syndrome focused on identifying a generic category of particular traits and behaviors associated with brain injury or dysfunction. This conceptual approach has been maintained in DSM-IV, although it sought to base its classification of personality changes solely upon consistently reported behavioral alterations. Suggestions to classify disorders upon anatomical localization (such as frontal lobe syndrome) were rejected. To date there has been little theoretical work attempting to integrate the dimensional perspectives used in the description of normal personality with the categorical approach used in the study of CNS disease and related personality disturbances.

**Definition** Personality change means that the person's fundamental means of interacting and behaving

have been altered; that is, traits that had been regular and consistent over a lifetime have changed. Personality change must be distinguished from the transient disturbances of behavior that frequently occur in reaction to environmental circumstances. When a true personality change occurs in adulthood, the clinician should always suspect brain injury or insult.

**History** The impact of brain insults on personality has long been recognized. John M. Harlow's description of personality change in Phineas Gage, who sustained a penetrating head injury, remains the classic description:

> He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. . . . In this regard his mind was radically changed, so decidedly that his friends and acquaintances said he was “no longer Gage.”

The frequency of association between brain injury and personality change prompted a search for a generic personality disorder applicable to all brain injury, as well as brain–locale-specific or disease-specific personality disorders. An example of the former is the organic personality disorder found in the earlier versions of DSM. Organic personality disorder was defined as a persistent disturbance of personality due to a specific organic factor involving affective instability, recurrent aggression or rage, impaired social judgment, apathy and indifference, or suspiciousness or paranoid ideation. The interictal personality disorder of temporal lobe epilepsy, characterized by hyperreligiosity, overinclusive speech and behavior, and sexual deviance, was originally presented as a disease-specific personality disorder that was thought to be of high validity. Subsequent studies did not find these traits specific for temporal lobe epilepsy or any other epilepsy. Attempts at defining locale-specific personality disorder have been hampered by difficulties in finding naturalistic human lesions that are indeed localized: Strokes, head trauma, and degenerative diseases, for example, rarely are confined to neat anatomical lobar boundaries.

Nonetheless, the most fruitful approach to delineating personality change disorders has come from the study of frontal lobe injury, where consistent and well-defined traits and behaviors have been associated with particular areas of brain injury. At least two distinct but overlapping secondary personality changes have been identified after injury to the orbitofrontal and frontal convexity areas. Frontal lobe dysfunction may play a key role in all personality and behavioral disturbances because there are vast networks of neural connections between specific areas of the frontal lobe and various limbic and subcortical structures. A similarly complex neuropsychological system suggests that the frontal lobe (more specifically, the prefrontal cortex) modulates many of the basic cognitive, linguistic, attentional, and perceptual processes that originate in other brain areas. Injury to the frontal lobes results in dysfunction in how basic cognitive functions, such as language or memory, are expressed.

**Comparative Nosology** DSM-I included a category of acute and chronic brain syndromes, defined as disorders due to a diffuse impairment of brain tissue function from any cause. DSM-II provided basic symptoms for a generic organic brain syndrome, such as impairments in orientation, memory, calculation, learning, and judgment, and lability and shallowness of affect. Although there was no specific category for secondary personality change, it would have been included in the nonpsychotic organic brain syndromes. DSM-III eliminated the unitary organic mental syndrome and allowed for a variety of organic syndromes in which an organic factor was judged etiologically related. Organic personality syndrome nonetheless required at least one of four specific characteristics, including lability, impulsivity, apathy, or suspiciousness; DSM-III-R added recurrent aggression to the list of criteria.

The limitations of the nosology are clear. Personality encompasses a broad range of traits and behaviors not limited to those specified in the organic personality disorder category. The disturbance of personality is identified not from the presence of any particular behavior or trait, but rather as a change from premorbid personality. DSM-IV has dropped the category of organic personality disorder and replaced it with personality change due to a general medical condition. The specific phenomenological criteria were dropped in favor of a general persistent personality disturbance that represents a change from the individual's previous characteristic personality pattern. Subtypes based on the particular phenomenology evident include labile type, disinhibited type, aggressive type, paranoid type, apathetic type, other type, combined type, and unspecified type.

**Epidemiology** The epidemiological difficulties in ascertaining cases of secondary personality changes are clear: No one particular behavior or trait is diagnostic; rather, a change in a patient's personality structure must be documented. Such documentation often requires recourse to an external informant because patients with personality change are frequently unreliable self-informants. The overinclusive range of personality traits enumerated in previous editions of DSM allowed researchers to pick and choose traits; in addition, the means of measuring them were not consistent from study to study. As a result, reliable incidence and prevalence figures for secondary personality change are not available. Specific personality trait changes for particular brain diseases—for example, passive and self-centered behaviors in dementia of the Alzheimer's type—have been reported; the studies reporting those results, however, have not been replicated, and it remains uncertain how the findings should be applied to other disorders.

**Etiology** The range of etiologies of secondary personality change is vast and diverse and may involve any of the basic pathological processes described in the previous section. Diseases that preferentially affect the frontal lobes or subcortical structures are more likely to manifest with prominent personality change. Head trauma is a common cause. Strokes involving the anterior communicating or middle cerebral arteries selectively damage frontal lobe structures, often resulting in personality change. The anterior communicating artery is also a common site for aneurysms, which can result in secondary personality change. Frontal lobe tumors, such as meningiomas and gliomas, can grow to considerable size before coming to medical attention, as they may be neurologically silent (i.e., without focal signs). Degenerative disorders affecting the frontal lobes can present with personality change long before cognitive symptoms are evident. Among progressive dementia syndromes, especially those with a subcortical pattern of degeneration, such as AIDS dementia complex, Huntington's disease, or

progressive supranuclear palsy, significant personality disturbance manifests often. Multiple sclerosis can impinge on the personality, reflecting subcortical white matter degeneration. Exposures to toxins with a predilection for white matter, such as irradiation, may also produce significant personality change disproportionate to the cognitive or motor impairment.

**Diagnosis and Clinical Features** The DSM-IV diagnostic criteria for personality change due to a general medical condition are listed in Table 10-52. The diagnosis of a secondary personality change rests entirely on the history. A clear and detailed description of the patient's premorbid personality must be obtained. This history usually is collected from an external informant who knew the patient at baseline as well as currently. The first task in evaluating the history is to determine whether a change in personality has indeed occurred or whether the current disruptive behaviors represent long-standing traits that have been exacerbated by a change in circumstance. In addition, delirium must be ruled out.

**Table 10-52** DSM-IV Diagnostic Criteria for Personality Change Due to a General Medical Condition

Once a diagnosis of a personality change has been established, the search for an etiological agent begins. An insidious and progressive course is suggestive of a degenerative process or a neoplasm. An abrupt onset of personality change is more suggestive of a vascular event or trauma. Risk factors for HIV infection should raise the suspicion of HIV or neurosyphilis infection. A complete history of toxic exposures, including alcohol and recreational drug use, environmental or occupational toxin exposures, and medications, should be obtained. The search for a causative agent can be aided by the presence of other evidence of brain dysfunction, such as motor abnormalities and cognitive impairment.

The particular form of a personality change may be helpful in determining the locus of injury or brain dysfunction, although much research remains to be done. The prefrontal cortex is often implicated in secondary personality change disorders. Two frontal lobe personality syndromes have been described, correlating with injury to the orbitofrontal and dorsolateral frontal cortical regions. Table 10-53 outlines the behavioral and personality changes associated with each. The anatomical designations for those syndromes may be misleading because frontal regions form rich neuronal networks with subcortical and limbic structures. Subcortical dementia also is characterized by significant personality deteriorations, such as apathy, aspontaneity, and slowing. Patients with multiple sclerosis sometimes present with a euphoric personality, which probably reflects a disruption of the orbitofrontal subcortical network.

| Orbitofrontal | Frontopolar |
|---|---|
| Disinhibition | Apathy |
| Inappropriate jocularity | Indifference |
| Affective lability | Psychomotor slowing |
| Impulsivity | Inaction |

**Table 10-53** Frontal Lobe Personality Change Syndromes

Global degenerative processes, such as dementia of the Alzheimer's type, involve significant personality change that has been less well characterized. In general, there is a coarsening of the personality with loss of subtlety and finesse. An exacerbation of premorbid traits is possible, with a suspicious patient becoming paranoid or a flamboyant patient becoming histrionic. Agitation or aggression is a common concomitant of brain disease. When they occur in a patient with a premorbid history of violence and a short temper, it may be difficult to determine if a secondary personality change has occurred, even when CNS dysfunction is evident.

Laboratory evaluation for secondary personality change is the same as for other secondary disorders. The most important element is informed clinical suspicion regarding specific disease processes.

**Differential Diagnosis** Secondary personality change must be differentiated from adjustment disorders occurring, for example, in response to environmental stressors or major medical disorders. Apathetic and amotivational symptoms in patients with dorsolateral frontal lesions may be mistaken for major depressive disorder. The former can be distinguished by a lack of pervasive dysphoria, intact neurovegetative function, and the absence of self-disparagement and hopelessness. Euphoria and disinhibition with the orbitofrontal syndrome may be ascribed to mania. The orbitofrontal syndrome, however, does not display heightened motor activity, excessive energy, and disrupted sleep; neither does it follow the cyclical course of bipolar I disorder but rather produces a persistent and consistent clinical picture.

**Course and Prognosis** The course of and prognosis of secondary personality syndromes depend on the course of the etiological systemic or cerebral disorder. Personality change secondary to mass lesions or hydrocephalus can improve dramatically with surgery, chemotherapy, or radiation therapy. However, each of these treatments may result in a different personality change syndrome. Personality change secondary to head trauma may improve slowly and gradually over the course of months or years, although residual disturbances may remain. Personality change due to degenerative processes can be most disruptive early in the disease process when the patient retains a measure of volition and control of motor capacities. Ironically, management of such patients may ease as the disease progresses, when the personality evolves into greater apathy, unresponsiveness, and akinesia. Personality change associated with epilepsy can improve dramatically with seizure control by pharmacotherapy or surgery.

**Treatment** Treatment for secondary personality syndromes is first directed toward correcting the underlying etiology. Symptomatic treatments as a group have been marginally effective at best. Lithium carbonate, carbamazepine, and valproic acid have been used for the control of affective lability and impulsivity. Aggression or explosiveness may be treated with lithium, anticonvulsant medications, or a combination of lithium and an anticonvulsant agent. Centrally active β-adrenergic receptor antagonists, such as propranolol (Inderal), have some efficacy as well. Antipsychotic medications are no more effective in the dampening of aggression than the previously mentioned agents, induce greater discomfort, and introduce the risk of tardive dyskinesia. Apathy and inertia have occasionally improved with psychostimulant agents. Because cognition and verbal skills may be preserved in patients with secondary personality changes, they may be candidates for psychotherapy. Families should be involved in the therapy process, with a focus on education and understanding the origins of the patient's inappropriate behaviors and coarsening. Issues such as competency, disability, and advocacy are frequently of clinical concern in those patients in light of the unpredictable and pervasive behavior change.

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**Table 10-1** DSM-IV Cognitive Disorders

| |
|---|
| Delirium |
| Delirium due to a general medical condition |
| Substance-induced delirium |
| Delirium due to multiple etiologies |
| Delirium not otherwise specified |
| Dementia |
| Dementia of the Alzheimer's type |
| Vascular dementia |
| Dementia due to other general medical conditions |
| Dementia due to HIV disease |
| Dementia due to head trauma |
| Dementia due to Parkinson's disease |
| Dementia due to Huntington's disease |
| Dementia due to Pick's disease |
| Dementia due to Creutzfeldt-Jakob disease |
| Dementia due to other general medical conditions |
| Substance-induced persisting dementia |
| Dementia due to multiple etiologies |
| Dementia not otherwise specified |
| Amnestic disorders |
| Amnestic disorder due to a general medical condition |
| Substance-induced persisting amnestic disorder |
| Amnestic disorder not otherwise specified |
| Cognitive disorder not otherwise specified |

**Table 10-2** Historical Periods in Neuropsychiatry

| | |
|---|---|
| 1845–1865 | Griesinger—Integration I |
| 1865–1900 | Neuropathological and descriptive psychiatry |
| 1900–1930 | Gradual transition I |
| 1930–1950 | Ferment |
| 1950–1965 | Psychodynamic era (United States) |
| 1965–present | Gradual transition II |
| The future | Integration II |


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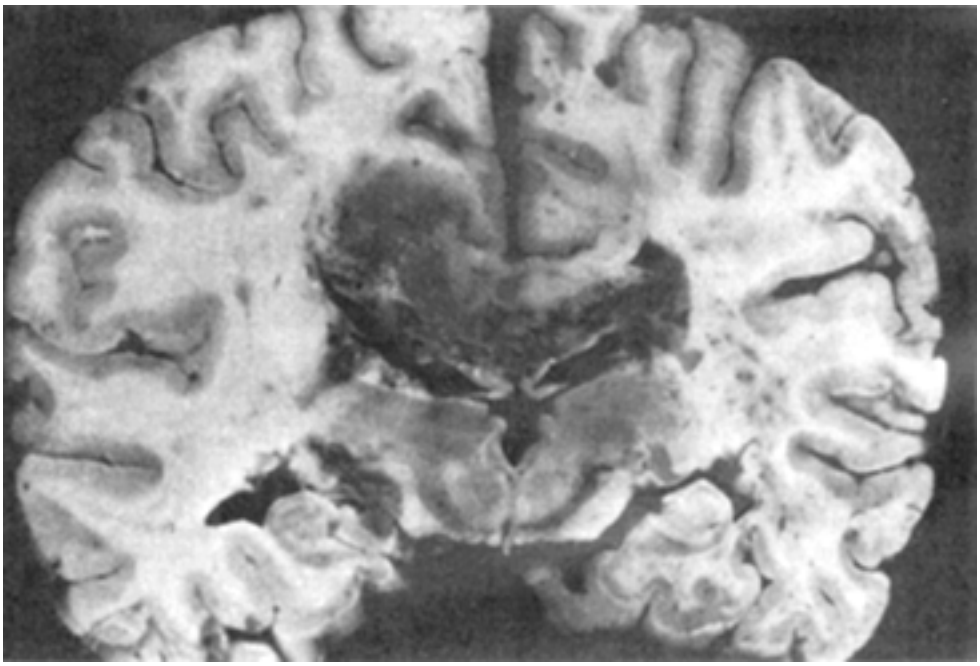

**FIGURE 10-2** Glioblastoma multiforme. The massive tumor crosses the midline in the corpus callosum. (Reprinted with permission from Hirano A: *A Guide Neuropathology*. Igaku-Shoin, New York, 1981.)

**Table 10-3** Neuropsychiatric Mental Status Examination

**A. General Description**
1. General appearance, dress, sensory aids (glasses, hearing aid)
2. Level of consciousness and arousal
3. Attention to environment
4. Posture (standing and seated)
5. Gait
6. Movements of limbs, trunk, and face (spontaneous, resting, and after instruction)
7. General demeanor (including evidence of responses to internal stimuli)
8. Response to examiner (eye contact, cooperation, ability to focus on interview process)
9. Native or primary language

**B. Language and Speech**
1. Comprehension (words, sentences, simple and complex commands, and concepts)
2. Output (spontaneity, rate, fluency, melody or prosody, volume, coherence, vocabulary, paraphasic errors, complexity of usage)
3. Repetition
4. Other aspects
   a. Object naming
   b. Color naming
   c. Body part identification
   d. Ideomotor praxis to command

**C. Thought**
1. Form (coherence and connectedness)
2. Content
   a. Ideational (preoccupations, overvalued ideas, delusions)
   b. Perceptual (hallucinations)

**D. Mood and Affect**
1. Internal mood state (spontaneous and elicited; sense of humor)
2. Future outlook
3. Suicidal ideas and plans
4. Demonstrated emotional status (congruence with mood)

**E. Insight and Judgment**
1. Insight
   a. Self-appraisal and self-esteem
   b. Understanding of current circumstances
   c. Ability to describe personal psychological and physical status
2. Judgment
   a. Appraisal of major social relationships
   b. Understanding of personal roles and responsibilities

**F. Cognition**

status
2. Judgment
   a. Appraisal of major social relationships
   b. Understanding of personal roles and responsibilities

**F. Cognition**

1. Memory
   a. Spontaneous (as evidenced during interview)
   b. Tested (incidental, immediate repetition, delayed recall, cued recall, recognition; verbal, nonverbal; explicit, implicit)
2. Visuospatial skills
3. Constructional ability
4. Mathematics
5. Reading
6. Writing
7. Fine sensory function (stereognosis, graphesthesia, two-point discrimination)
8. Finger gnosis
9. Right-left orientation
10. "Executive functions"
11. Abstraction

---

**Table 10-4** Screening Laboratory Tests

**General Tests**

Complete blood cell count
Erythrocyte sedimentation rate
Electrolytes
Glucose
Blood urea nitrogen and serum creatinine
Liver function tests
Serum calcium and phosphorus
Thyroid function tests
Serum protein
Levels of all drugs
Urinalysis
Pregnancy test for women of childbearing age
Electrocardiography

**Ancillary Laboratory Tests**

*Blood*
- Blood cultures
- Rapid plasma reagin test
- HIV testing (ELISA and Western blot)
- Serum heavy metals
- Serum copper
- Ceruloplasmin
- Serum $B_{12}$, RBC folate levels

*Urine*
- Culture
- Toxicology
- Heavy metal screen

*Electrography*
- Electroencephalography
- Evoked potentials
- Polysomnography
- Nocturnal penile tumescence

*Cerebrospinal fluid*
- Glucose, protein
- Cell count
- Cultures (bacterial, viral, fungal)
- Cryptococcal antigen
- Venereal Disease Research Laboratories assay

*Radiography*
- Computed tomography
- Magnetic resonance imaging
- Positron emission tomography
- Single photon emission computed tomography

*Radiography*
Computed tomography
Magnetic resonance imaging
Positron emission tomography
Single photon emission computed tomography


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Kaplan & Sadock's Comprehensive Textbook of Psychiatry

**Table 10-5** Pathophysiological Mechanisms of Brain Injury After Head Trauma

| |
|---|
| **Direct Effects** |
| Contusion underlying point of trauma (coup) |
| Contusion linearly opposite point of trauma (contracoup) |
| Compression from overlying depressed skull fracture |
| Compression from overlying hematoma |
| **Indirect Effects** |
| Diffuse impact damage |
| Widespread damage in cerebral white matter |
| Discrete lesions in corpus callosum |
| Discrete lesions in rostral brainstem |
| Common cortical contusions independent of direction of impact |
| Orbitofrontal |
| Anterior temporal |
| Frontopolar |
| Secondary cerebral processes |
| Cerebral edema |
| Increased intracranial pressure with central herniation (Duret's hemorrhages) |
| Increased intracranial pressure with uncal herniation and posterior cerebral artery entrapment (medial occipital infarction) |
| Multifocal ischemic changes |
| Contributing secondary systemic processes |
| Shock (blood loss, ruptured viscera, sepsis, etc.) with hypotension |
| Pulmonary failure with anoxia |
| Long bone fracture with fat emboli |

Adapted from Alexander MP: Traumatic brain injury. In *Psychiatric Aspects of Neurologic Disease,* vol 2, DF Benson, D Blumer, editors. Grune & Stratton, New York, 1982.

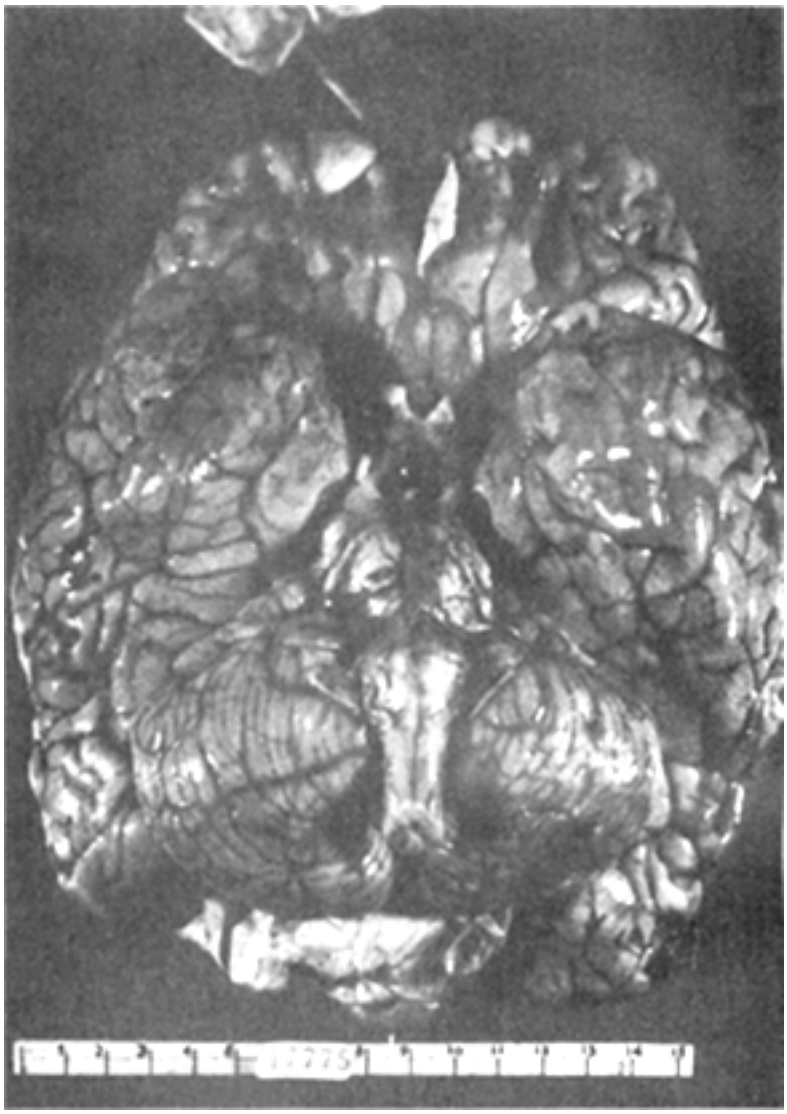

**FIGURE 10-1** Severe contusion of the frontal poles has resulted in their atrophy and distortion. (Courtesy of H. M. Zimmerman, M.D.)

**Table 10-6** Frequently Observed Features of Concussion

| |
|---|
| Vacant stare (befuddled facial expression) |
| Delayed verbal and motor responses (slow to answer questions or follow instructions) |
| Confusion and inability to focus attention (easily distracted and unable to follow through with normal activities) |
| Disorientation (walking in the wrong direction; unaware of time, date, and place) |
| Slurred or incoherent speech (making disjointed or incomprehensible statements) |
| Gross observable incoordination (stumbling, inability to walk tandem/straight line) |
| Emotions out of proportion to circumstances (distraught, crying for no apparent reason) |
| Memory deficits (exhibited by repeatedly asking a question that has already been answered, or inability to memorize and recall 3 of 3 objects in 5 minutes) |
| Any period of loss of consciousness (paralytic coma, unresponsiveness to arousal) |

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**Table 10-7** Symptoms of Concussion

| |
|---|
| Early (minutes and hours): |
| Headache |
| Dizziness or vertigo |
| Lack of awareness of surroundings |
| Nausea or vomiting |
| Late (days to weeks): |
| Persistent low-grade headache |
| Light-headedness |
| Poor attention and concentration |
| Memory dysfunction |
| Easy fatigability |
| Irritability and low frustration tolerance |
| Intolerance of bright lights or difficulty focusing vision |
| Intolerance of loud noises, sometimes ringing in the ears |
| Anxiety and/or depressed mood |
| Sleep disturbance |

Reprinted with permission from Quality Standards Committee, American Academy of Neurology (chief authors, Kelly JP, Rosenburg JH): The management of concussion in sports (summary statement). Neurology *48*:582, 1997.

**Table 10-8** Gradations of Concussion

| | |
|---|---|
| Grade 1 | Transient confusion<br>No loss of consciousness<br>Concussion symptoms or mental status abnormalities resolve in 15 minutes |
| Grade 2 | Transient confusion<br>No loss of consciousness<br>Symptoms resolve in >15 minutes |
| Grade 3 | Any loss of consciousness |

**Table 10-9** DSM-IV Research Criteria for Postconcussional Disorder

A. A history of head trauma that has caused significant cerebral concussion.
   **Note:** The manifestations of concussion include loss of consciousness, posttraumatic amnesia, and less commonly, posttraumatic onset of seizures. The specific method of defining this criterion needs to be established by further research.

B. Evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention (concentrating, shifting focus of attention, performing simultaneous cognitive tasks) or memory (learning or recalling information).

C. Three (or more) of the following occur shortly after the trauma and last at least 3 months.
   (1) becoming fatigued easily
   (2) disordered sleep
   (3) headache
   (4) vertigo or dizziness
   (5) irritability or aggression on little or no provocation
   (6) anxiety, depression, or affective lability
   (7) changes in personality (e.g., social or sexual inappropriateness)
   (8) apathy or lack of spontaneity

D. The symptoms in criteria B and C have their onset following head trauma or else represent a substantial worsening of preexisting symptoms.

E. The disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning. In school-age children, the impairment may be manifested by a significant worsening in school or academic performance dating from the trauma.

F. The symptoms do not meet criteria for dementia due to head trauma and are not better accounted for by another mental disorder (e.g., amnestic disorder due to head trauma, personality change due to head trauma).

**Table 10-10** ICD-10 Diagnostic Criteria for Personality and Behavioral Disorders Due to Brain Disease, Damage and Dysfunction

G1. There must be objective evidence (from physical and neurological examination and laboratory tests) and/or history of cerebral disease, damage, or dysfunction.

G2. There is no clouding of consciousness or significant memory deficit.

G3. There is insufficient evidence for an alternative causation of the personality or behavior disorder that would justify its placement in disorders of adult personality and behavior category.

Organic personality disorder

A. The general criteria for personality and behavioral disorders due to brain disease, damage, and dysfunction must be met.

B. At least three of the following features must be present over a period of 6 months or more:
   (1) Consistently reduced ability to persevere with goal-directed activities, especially those involving relatively long periods and postponed gratification;
   (2) one or more of the following emotional changes:
      (a) emotional lability (uncontrolled, unstable, and fluctuating expression of emotions);
      (b) euphoria and shallow, inappropriate jocularity, unwarranted by the circumstances;
      (c) irritability and/or outbursts of anger and aggression;
      (d) apathy;
   (3) disinhibited expression of needs or impulses without consideration of consequences or of social conventions (the individual may engage in dissocial acts such as stealing, inappropriate sexual advances, or voracious eating, or exhibit extreme disregard for personal hygiene);
   (4) cognitive disturbances, typically in the form of:
      (a) excessive suspiciousness and paranoid ideas;
      (b) excessive preoccupation with a single theme such as religion, or rigid categorization of other people's behavior in terms of "right" and "wrong";
   (5) marked alteration of the rate and flow of language production, with features such as circumstantiality, overinclusiveness, viscosity, and hypergraphia;
   (6) altered sexual behavior (hyposexuality or change in sexual preference).

Specification of features for possible subtypes

*Option 1.* A marked predominance of the symptoms in criteria (1) and (2)(d) is thought to define a pseudoretarded or apathetic type; a predominance of (1), (2)(c), and (3) is considered a pseudopsychopathic type; and a combination of (4), (5) and (6) is regarded as characteristic of the limbic epilepsy personality syndrome. None of these entities has yet been sufficiently validated to warrant a separate description.

*Option 2.* If desired, the following types may be specified: labile type, disinhibited type, aggressive type, apathetic type, paranoid type, mixed type, and other.

Postencephalitic syndrome

A. The general criteria for personality and behavioral disorders due to brain disease, damage, and dysfunction must be met.

B. At least one of the following residual neurological dysfunctions must be present:
   (1) paralysis;
   (2) deafness;
   (3) aphasia;
   (4) constructional apraxia;
   (5) acalculia.

C. The syndrome is reversible, and its duration rarely exceeds 24 months.

*Comments*

Criterion C constitutes the main difference between this disorder and organic personality disorder.

Residual symptoms and behavioral change following either viral or bacterial encephalitis are nonspecific and do not provide a sufficient basis for a clinical diagnosis. They may include: general malaise, apathy, or irritability; some lowering of cognitive functioning (learning difficulties); disturbances in the sleep-wake pattern; or altered sexual behavior.

Postconcussional syndrome

*Note.* The nosological status of this syndrome is uncertain, and criterion G1 of the introduction to this rubric is not always ascertainable. However, for those undertaking research into this condition, the following criteria are recommended:

A. The general criteria of personality and behavioral disorders due to brain disease, damage, and dysfunction must be met.

B. There must be a history of head trauma with loss of consciousness, preceding the onset of symptoms by a period of up to 4 weeks. (Objective EEG, brain imaging, or oculonystagmographic evidence for brain damage may be lacking.)

C. At least three of the following features must be present:
   (1) complaints of unpleasant sensations and pains, such as headache dizziness (usually lacking the features of true vertigo), general malaise, and excessive fatigue, or noise intolerance;
   (2) emotional changes, such as irritability, emotional lability (both easily provoked or exacerbated by emotional excitement or stress), or some degree of depression and/or anxiety;
   (3) subjective complaints of difficulty in concentration and in performing mental tasks, and of memory problems (without clear objective evidence, e.g., psychological tests, of marked impairment);
   (4) insomnia;
   (5) reduced tolerance to alcohol;
   (6) Preoccupation with the above symptoms and fear of permanent brain damage, to the extent of hypochondriacal, overvalued ideas and adoption of a sick role.

Other organic personality and behavioral disorders due to brain disease, damage, and dysfunction

Brain disease, damage, or dysfunction may produce a variety of cognitive, emotional personality, and behavioral disorders, some of which may not be classifiable under organic personality disorder, postencephalitic syndrome, postconcussional syndrome. However, since the nosological status of the tentative syndromes in this area is uncertain, they should be coded as "other." A fifth character may be added, if necessary, to identify presumptive individual entities.

Unspecified organic personality and behavioral disorder due to brain disease, damage, and dysfunction

(5) acalculia.

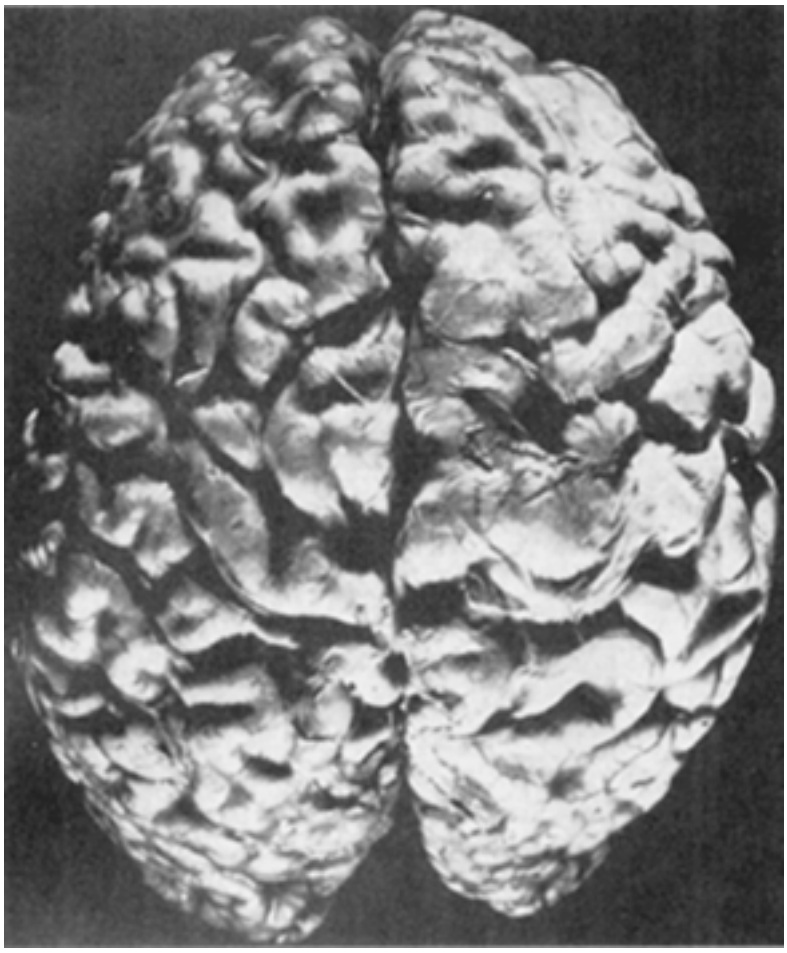

**FIGURE 10-3** Paretic neurosyphilis. Thickening of the meninges and atrophy of the cerebral convolutions. (Reprinted with permission from Merritt HH, Adams RD, Solomon HC: *Neurosyphilis*. Oxford University Press, New York, 1946.)

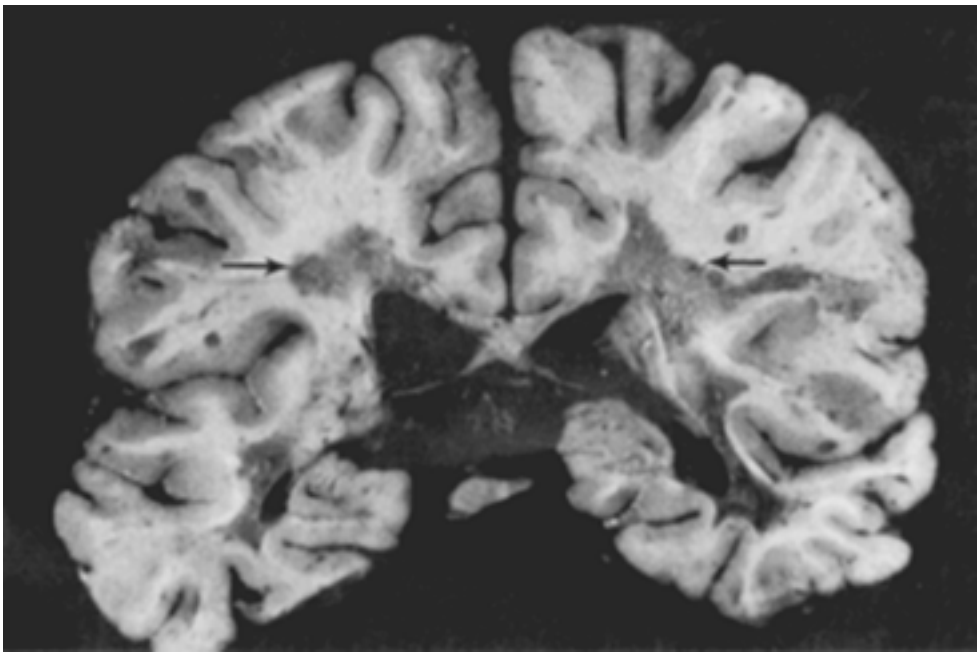

**FIGURE 10-4** Multiple sclerosis. Coronal section of cerebral hemispheres showing large, sharply demarcated plaques adjacent to the bodies of the lateral ventricles (arrows). Other plaques are found adjacent to the temporal horns and smaller plaques are present in the subcortical white matter and centra semiovales. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)

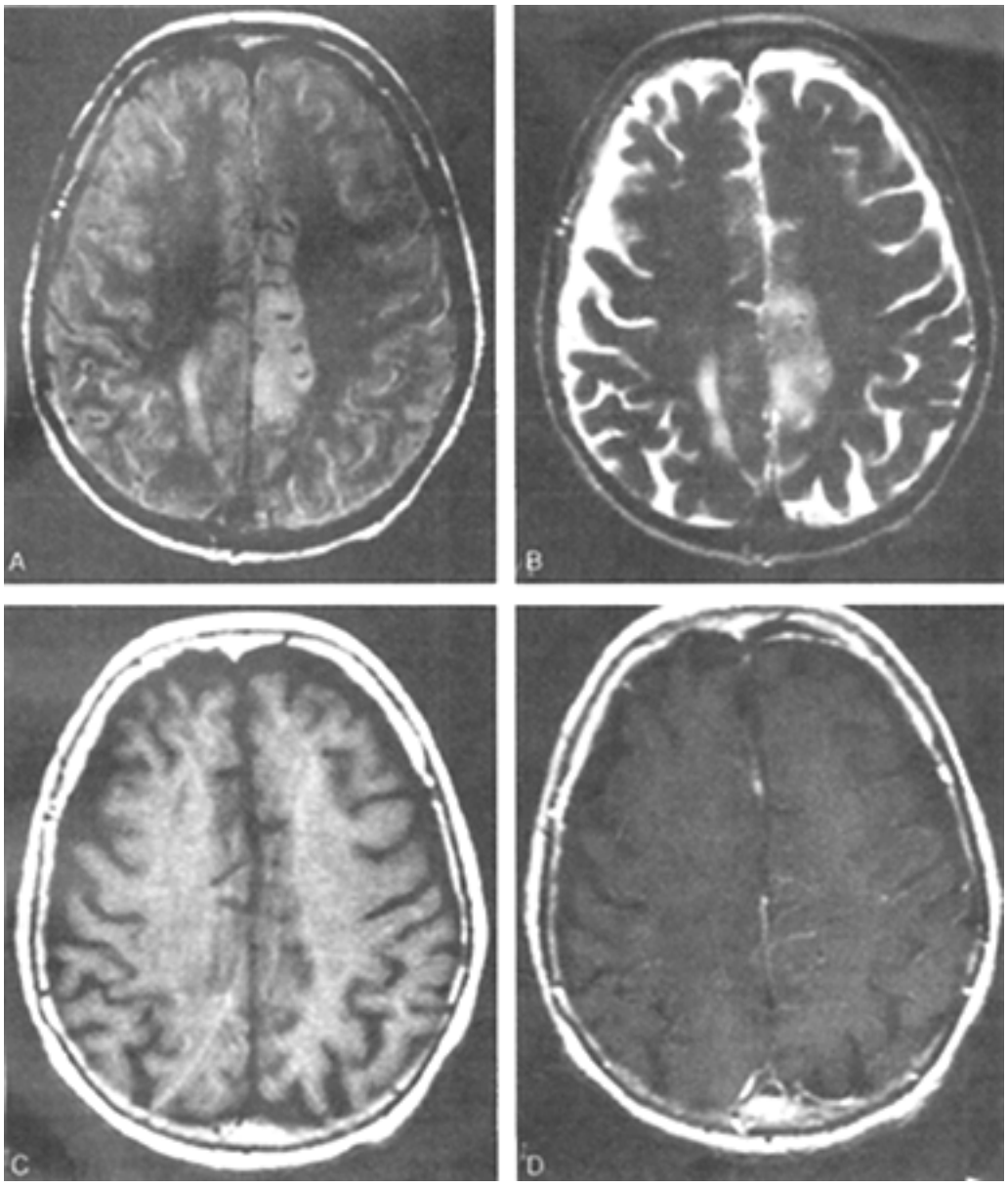


**FIGURE 10-5** Acute cortical infarction. **A** and **B**, Proton-density and T2-weighted axial MRI scans show increased signal intensity within the medial cortex of left frontal and parietal lobes. Note swelling of gray matter and prominence of blood vessels within this lesion. **C** and **D** T1-weighted axial MRI scans before and after gadolinium administration demonstrate several linear foci of contrast enhancement within the area of infarction in the left frontal and parietal lobes, most consistent with enhancing arterial branches. Contrast enhancement of arterial branches is consistent with static blood flow within the infarct, and generally is seen only within the first few hours to 5 days after the onset of acute infarction. (Reprinted with permission from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, Baltimore, 1995.)

**Table 10-11** Types of Cerebrovascular Events

| |
|---|
| **Thrombotic** |
| Most commonly related to atherosclerotic stenosis or occlusion of cerebral vessels |
| May or may not be preceded by warning transient ischemic attacks (TIAs) |
| Onset may be gradual, stuttering, or acute |
| Produces ischemic infarction |
| **Embolic** |
| Emboli may arise from cardiac (thrombus, valve vegetation, atheromatous plaque) or carotid (thrombus) origin |
| Onset is typically rapid without warning TIAs |
| Produces ischemic, hemorrhagic, or mixed infarction |
| **Hemorrhagic** |
| Extradural—typically from trauma to middle meningeal artery |
| Subdural—from rupture of bridging veins |
| Subarachnoid—from ruptured saccular aneurysms (e.g., in circle of Willis) |
| Intracerebral—types include hypertensive, ruptured arteriovenous malformations; other contributors include hemorrhagic diatheses, vasculitis, bleeding into cerebral tumors, and septic emboli |
| Onset is typically rapid with further progression, without prior warning |
| **Lacunar** |
| Refers to occlusion of small perforating arteries, producing deep, small (2–15 mm) cavitary infarcts called *lacunes* |
| Associated with hypertension and atherosclerosis |
| Onset may be rapid, followed by partial or complete recovery, but accumulated multiple lacunes may produce secondary psychiatric syndromes |

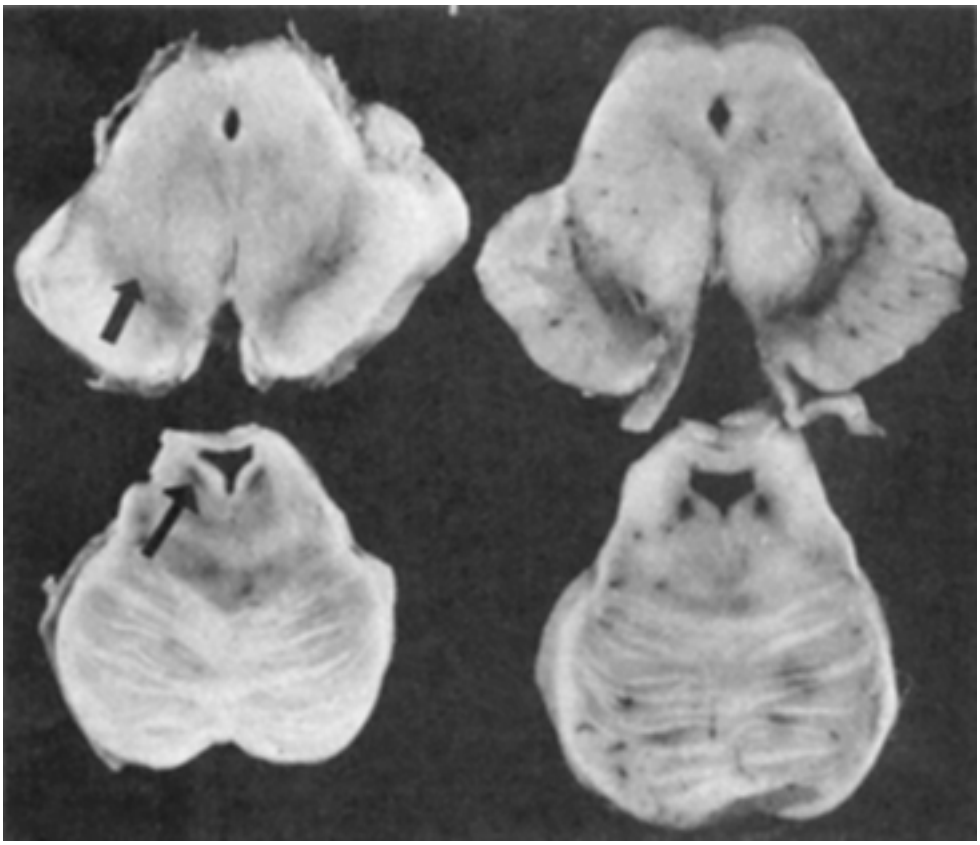

**FIGURE 10-11** Parkinson's disease. Section of midbrain and pons showing depigmentation of substantia nigra and locus ceruleus in Parkinson's disease on left (arrows) and normal substantia nigra and locus ceruleus on right. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)

**Table 10-12** Examples of Developmental and Hereditary Disorders With Neuropsychiatric Manifestations

| Syndrome | Etiology | Onset of Manifestations | Neuropsychiatric Findings |
|---|---|---|---|
| Down's syndrome | Trisomy of chromosome 21 | Lifelong | Dysmorphic facies; moderate to severe mental retardation, dementia in fourth to fifth decades of life |
| Fragile X syndrome | X chromosome heteromorphism | Lifelong | Males: dysmorphic facies, autism, moderate to severe mental retardation, macroorchidism; females: mild mental retardation hyperactivity, affective disorder, developmental Gerstmann syndrome |
| Prader-Willi syndrome | Partial deletion of chromosome 15 | Lifelong | Hyperphagia; lability; obesity; mild to moderate mental retardation |
| Learning disorder of the right hemisphere | Pre-, peri-, or postnatal insult versus genetic | Emerges in childhood | Normal intelligence but marked verbal/performance discrepancy; pathological shyness; difficulty with perception and appreciation of affect |
| Acute intermittent porphyria | Autosomal dominant with incomplete penetrance | Emerges after puberty, usually in third decade | Intermittent attacks with abdominal pain, polyneuropathy, seizures and delirium |
| Metachromatic leukodystrophy | Autosomal recessive deficiency of enzyme arylsulfatase A | Juvenile and adult forms | Personality change; auditory hallucinations; paranoid and grandiose delusions early; dementia and neurological deterioration later |
| Adrenoleukodystrophy | X-linked recessive | Juvenile and adult forms | Delusions and hallucinations; Addison's disease |
| Olivopontocerebellar degeneration (OPCA) | Autosomal dominant | Juvenile and adult forms | Subcortical dementia |
| Huntington's disease | Autosomal dominant; chromosome 4 linkage | Juvenile and adult forms; adult more common | Subcortical dementia; major depressive disorder, bipolar disorder |

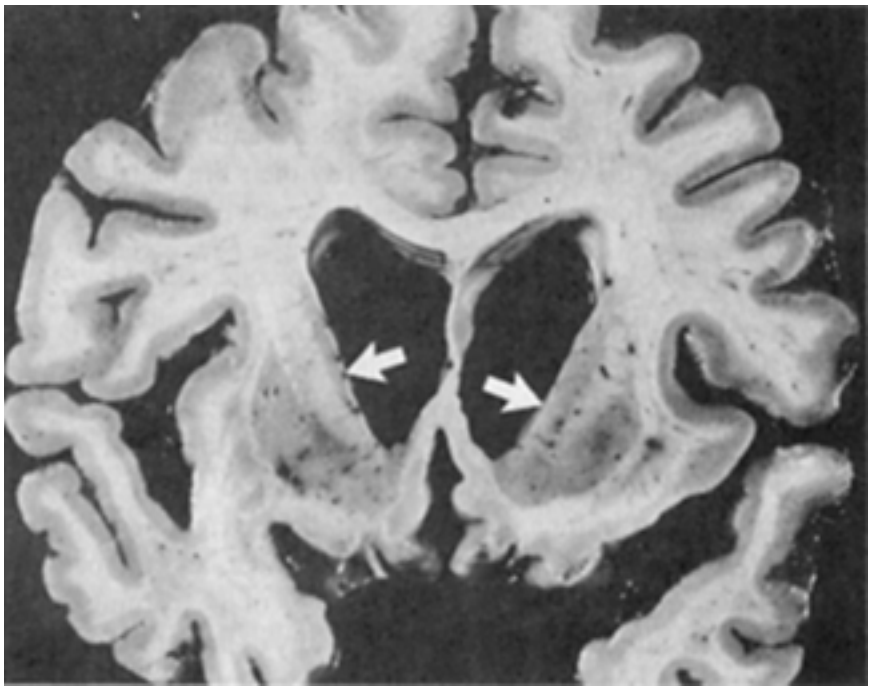

**FIGURE 10-6** Huntington's chorea. There is marked atrophy of the caudate nuclei (arrows) and mild dilatation of the lateral ventricles. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)

**Table 10-13** Classification of the Epilepsies

| |
|---|
| Primary generalized epilepsy |
| Tonic-clonic (grand mal) |
| Absence (petit mal) |
| Myoclonic |
| Other |
| Partial (focal) epilepsy |
| Simple (elementary) symptomatology |
| Focal motor |
| Focal sensory |
| Vegetative |
| Mixed |
| Complex symptomatology |
| Partial complex (psychomotor) |
| Secondary generalized |
| Unclassifiable |


FIGURE 12-1 *Progression of phases in epileptic seizure disorders.*

**FIGURE 10-7** Progression of phases in epileptic seizure disorders.

**Table 10-14** Neuropsychiatric Manifestations (in the Aura and Ictus) of Focal Epilepsy

| | |
|---|---|
| Sensory | Cognitive |
| Headache | Transient dysphasia |
| Focal pain | Speech automatisms |
| Paresthesia | Subjective confusion |
| Motor | Obsessional thinking |
| Nystagmus | Thought blocking |
| Head turning | Distortion of time sense |
| Scanning | Affective |
| Posturing | Fear |
| Stuttering | Anxiety |
| Autonomic | Sadness |
| Facial flushing | Embarrassment |
| Hot flashes | Placidity |
| Pallor | Guilt |
| Dizziness | Anger |
| Chest pain | Joy |
| Tinnitus | Elation |
| Perceptual | Other |
| Micropsia, macropsia | Genital sensations |
| Heightened auditory acuity | Sexual behaviors |
| Derealization, depersonalization | |
| Déjà vu, *jamais vu* | |
| Hallucinations (visual, auditory, olfactory, gustatory, and tactile) | |

**Table 10-15** Chronology* of Antiepileptic Drugs

| | |
|---|---|
| Conventional Drugs | |
| Phenobarbital | 1912 |
| Phenytoin | 1938 |
| Trimethadione | 1946 |
| Phensuximide | 1953 |
| Methsuximide | 1957 |
| Ethosuximide | 1960 |
| Benzodiazepines | 1965 |
| Carbamazepine | 1974 |
| Valproate | 1978 |
| New Drugs* | |
| Felbamate | 1993 |
| Gabapentin | 1994 |
| Lamotrigine | 1995 |
| Topiramate | 1997 |
| Tiagabine | 1997 |
| Vigabatrin | In Europe |
| Oxcarbazepine | In Europe |
| Loreciezole | In trials |
| Stiripentol | In trials |
| Zonisamide | In trials |

* Dates refer to U.S. introduction; lamotrigine was marketed earlier in Europe.
Adapted from Avoli M: Molecular mechanisms of antiepileptic drugs. Sci Med 4(4):58, 1997.

**Table 10-16** Antiepileptic Drugs

| | Effects on Voltage-Gated Channels | | | Effect on GABA Receptor | Effects on Excitatory Amino Acid Receptors | Indications |
|---|---|---|---|---|---|---|
| | Sodium | Calcium | Potassium | | | |
| Barbiturates | +/? | +/? | ? | + + | +/? | Broad-spectrum anticonvulsants |
| Benzodiazepines | +/? | – | ? | + + | – | Broad-spectrum anticonvulsants |
| Carbamazepine | + + | +/? | +/? | – | – | Partial seizures |
| Ethosuximide | – | + + (T-type) | – | – | – | Absence seizures |
| Felbamate | + | ? | ? | +/? | + + (NMDA) | Broad-spectrum anticonvulsant* |
| Gabapentin | +/? | – | ? | + | +/? | Partial seizures |
| Lamotrigine | + + | – | ? | – | +/? | Partial seizures/broad-spectrum |
| Oxcarbazepine | + | +/? | ? | – | – | Partial seizures |
| Phenytoin | + + | +/? | – | – | – | Partial seizures |
| Tiagabine | – | – | – | + + | – | Partial seizures |
| Topiramate | +/? | – | ? | +/? | + (Non-NMDA) | Partial seizures/broad-spectrum |
| Vigabatrin | – | – | ? | + + | – | Partial seizures/infantile spasms |
| Valproate | + | +/? | – | +/? | – | Broad-spectrum anticonvulsant |

* Felbamate is not a first-line treatment because of risk of aplastic anemia and hepatic failure.
+/? Shown but not defined
+ Established
+ + Well established
– Negative finding
? Unavailable data
Reprinted with permission from Avoli M: Molecular mechanisms of antiepileptic drugs. Sci Med 4(4):63, 1997.

**Table 10-17** Metabolic and Other Systemic Disturbances

| |
|---|
| Endocrine |
| Hypothyroidism or hyperthyroidism |
| Hypoparathyroidism or hyperparathyroidism |
| Sex hormones—too little, too much, or cycle-related |
| Hypocortisolemia or hypercortisolemia |
| Pheochromocytoma |
| Diabetes mellitus |
| Carcinoid syndrome |
| Pulmonary |
| Hypoxemia |
| Hypercarbia |
| Infections (pneumonia, bronchiectasis, abscess) |
| Restrictive lung diseases |
| Obstructive lung diseases |
| Tumors |
| Hematologic |
| Anemia |
| Polycythemia |
| Neoplasms |
| Hepatic |
| Liver failure due to any etiology |
| Renal |
| Renal failure due to any etiology |
| Infections |
| Neoplasms |
| Nutrition |
| Marasmus |
| Kwashiorkor |
| Vitamin deficiencies (thiamine, niacin, $B_{12}$, folate) |
| Dehydration |
| Miscellaneous |
| Hypoelectrolyte and hyperelectrolyte disturbances (especially sodium, potassium, phosphate, calcium, magnesium) |
| Hypoglycemia and hyperglycemia |
| Acidemia |
| Alkalemia |
| Porphyria |

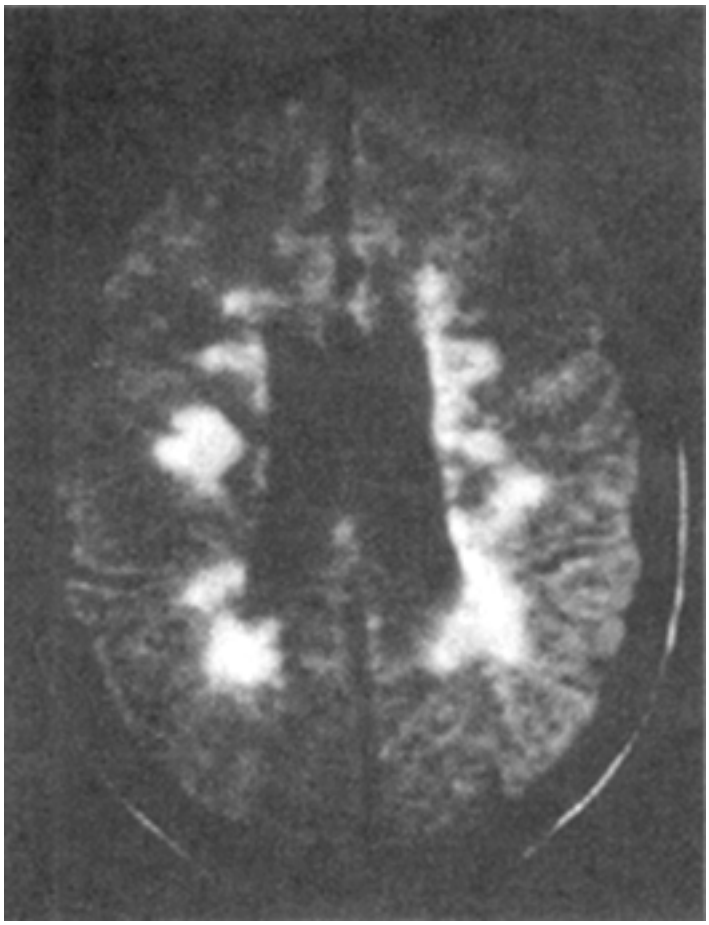

**FIGURE 10-8** MRI study of the head. Extensive confluent periventricular lesions are seen in a patient with multiple sclerosis. The corresponding CT scan was normal. (Reprinted with permission from Lukes SA, Crooks LE, Aminoff MJ, Kaufman L, Panitch HS, Mills C, Norman D: Nuclear magnetic resonance imaging in multiple sclerosis. Ann Neurol *13*:596, 1983.)

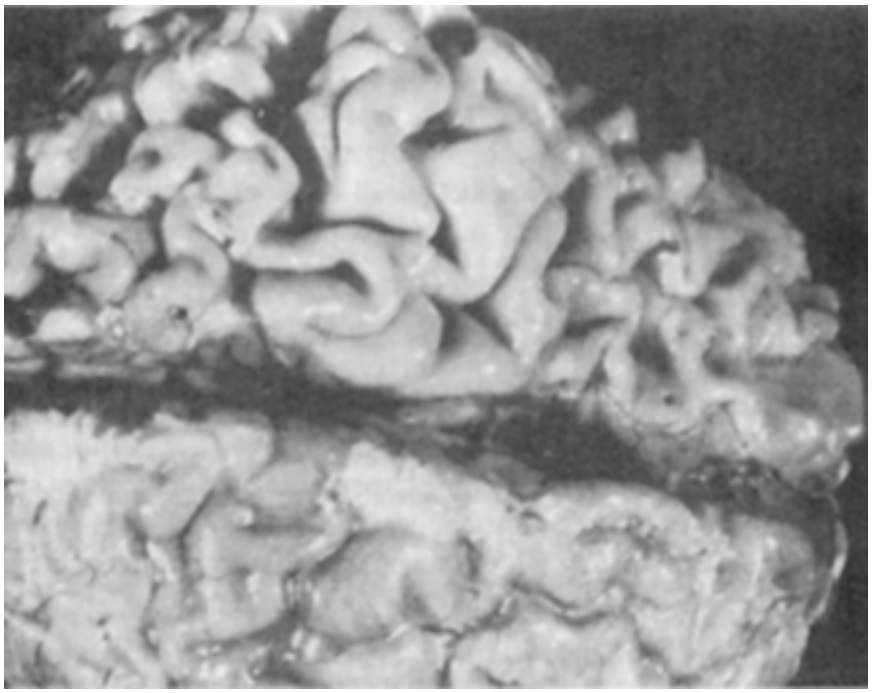

**FIGURE 10-9** Alzheimer's disease. View of exposed left cortex showing severe atrophy. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)

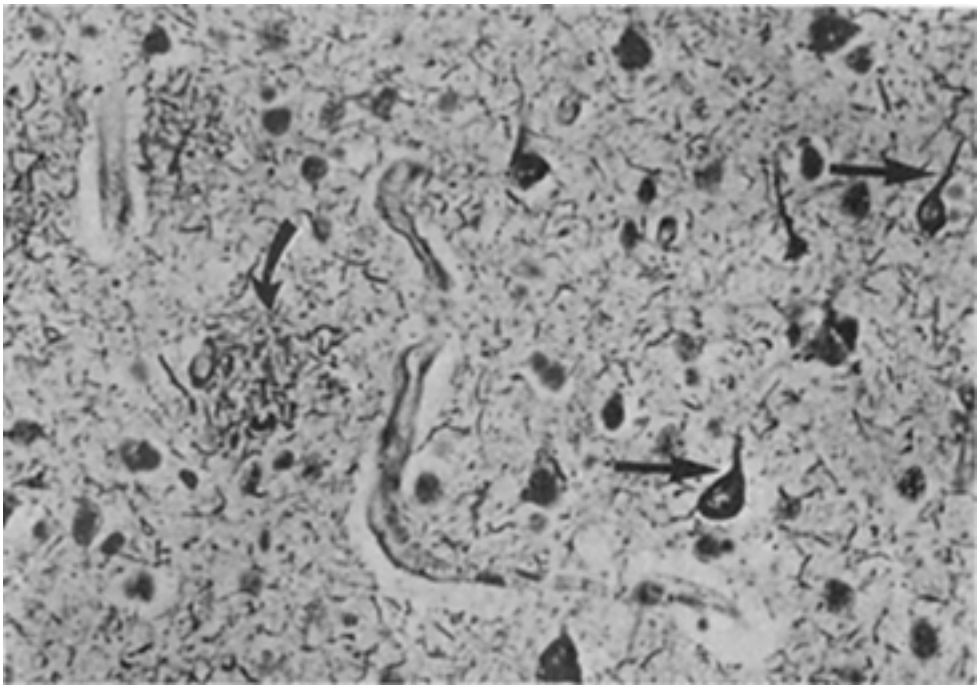

**FIGURE 10-10** Light micrograph of the cerebral cortex showing neurofibrillary tangles (arrows) and senile plaque (curved arrow) in Alzheimer's disease. (Reprinted with permission from Golden A, Powell DE, Jennings CD: *Pathology: Understanding Human Disease*, ed 2. Williams & Wilkins, Baltimore, 1985.)

**Table 10-18** Pathological Features Associated With Dementia With Lewy Bodies

| |
|---|
| Essential for diagnosis |
| Lewy bodies |
| Associated but not essential |
| Lewy-related neurites |
| Plaques (all morphological types) |
| Neurofibrillary tangles |
| Regional neuronal loss—especially brainstem (substantia nigra and locus coeruleus) and nucleus basalis of Meynert |
| Microvacuolation (spongiform change) and synapse loss |
| Neurochemical abnormalities and neurotransmitter deficits |

Reprinted with permission from McKeith IG, Galasko D, Kosaka K, et al: For the Consortium on Dementia with Lewy Bodies. Neurology *47*:1113, 1996.

**Table 10-19** Consensus Criteria for the Clinical Diagnosis of Probable and Possible Dementia With Lewy Bodies

1. The central feature required for a diagnosis of dementia with Lewy bodies is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for a diagnosis of probable dementia with Lewy bodies, and one is essential for possible dementia with Lewy bodies:
   a. Fluctuating cognition with profound variations in attention and alertness
   b. Recurrent visual hallucinations that are typically well formed and detailed
   c. Spontaneous motor features of parkinsonism
3. Features supportive of the diagnosis are:
   a. Repeated falls
   b. Syncope
   c. Transient loss of consciousness
   d. Neuroleptic sensitivity
   e. Systematized delusions
   f. Hallucinations in other modalities
4. A diagnosis of dementia with Lewy bodies is less likely in the presence of:
   a. Stroke disease, evident as focal neurologic signs or on brain imaging
   b. Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

Reprinted with permission from McKeith IG, Galasko D, Kosaka K, et al: For the Consortium on Dementia with Lewy Bodies. Neurology *47*:1113, 1996.

**Table 10-20** Causes of Delirium

| |
|---|
| Drug intoxication |
| Anticholinergics |
| Lithium |
| Antiarrhythmics (e.g., lidocaine) |
| $H_2$-receptor blockers |
| Sedative-hypnotics |
| Alcohol |
| Drug withdrawal |
| Alcohol |
| Sedative-hypnotics |
| Tumor |
| Primary cerebral |
| Trauma |
| Cerebral contusion (as an example) |
| Subdural hematoma |
| Infection |
| Cerebral (e.g., meningitis, encephalitis, HIV, syphilis) |
| Systemic (e.g., sepsis, urinary tract infection, pneumonia) |
| Cardiovascular |
| Cerebrovascular (e.g., infarcts, hemorrhage, vasculitis) |
| Cardiovascular (e.g., low-output states, congestive heart failure, shock) |
| Physiological or metabolic |
| Hypoxemia, electrolyte disturbances, renal or hepatic failure, hypo- or hyperglycemia, postictal states (as examples) |
| Endocrine |
| Thyroid or glucocorticoid disturbances (as examples) |
| Nutritional |
| Thiamine or vitamin $B_{12}$ deficiency, pellagra (as examples) |

**Table 10-21** DSM-IV Diagnostic Criteria for Delirium Due to a General Medical Condition

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

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

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

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

**Coding note:** Include the name of the general medical condition on Axis I, e.g., delirium due to hepatic encephalopathy; also code the general medical condition on Axis III.

**Table 10-22** DSM-IV Diagnostic Criteria for Substance Intoxication Delirium

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

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

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

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

**Note:** This diagnosis should be made instead of a diagnosis of substance intoxication only when the cognitive symptoms are in excess of those usually associated with the intoxication syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

**Note:** The diagnosis should be recorded as substance-induced delirium if related to medication use.

*Code:* [Specific substance] intoxication delirium (Alcohol; amphetamine [or amphetamine-like substance]; cannabis; cocaine; hallucinogen; inhalant; opioid; phencyclidine [or phencyclidine-like substance]; sedative, hypnotic, or anxiolytic; other [or unknown] substance [e.g., cimetidine, digitalis, benztropine])

**Table 10-23** DSM-IV Diagnostic Criteria for Substance Withdrawal Delirium

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

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

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

D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.

**Note:** This diagnosis should be made instead of a diagnosis of substance withdrawal only when the cognitive symptoms are in excess of those usually associated with the withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

*Code:* [Specific substance] withdrawal delirium: (Alcohol; sedative, hypnotic, or anxiolytic; other [or unknown] substance).

**Table 10-24** DSM-IV Diagnostic Criteria for Delirium Due to Multiple Etiologies

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

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

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

D. There is evidence from the history, physical examination, or laboratory findings that the delirium has more than one etiology (e.g., more than one etiological general medical condition, a general medical condition plus substance intoxication or medication side effect).

**Coding note:** Use multiple codes reflecting specific delirium and specific etiologies, e.g., delirium due to viral encephalitis, alcohol withdrawal delirium.

**Table 10-25** DSM-IV Diagnostic Criteria for Delirium Not Otherwise Specified

This category should be used to diagnose a delirium that does not meet criteria for any of the specific types of delirium described in this section.

Examples include

1. A clinical presentation of delirium that is suspected to be due to a general medical condition or substance use but for which there is insufficient evidence to establish a specific etiology.
2. Delirium due to causes not listed in this section (e.g., sensory deprivation).

**Table 10-26** ICD-10 Diagnostic Criteria for Delirium, Not Induced by Alcohol and Other Psychoactive Substances

A. There is clouding of consciousness, i.e., reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.

B. Disturbance of cognition is manifest by both:
   (1) impairment of immediate recall and recent memory, with relatively intact remote memory;
   (2) disorientation in time, place, or person.

C. At least one of the following psychomotor disturbances is present:
   (1) rapid, unpredictable shifts from hypoactivity to hyperactivity;
   (2) increased reaction time;
   (3) increased or decreased flow of speech;
   (4) enhanced startle reaction.

D. There is disturbance of sleep or of the sleep-wake cycle, manifest by at least one of the following:
   (1) insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle;
   (2) nocturnal worsening of symptoms;
   (3) disturbing dreams and nightmares, which may continue as hallucinations or illusions after awakening.

E. Symptoms have rapid onset and show fluctuations over the course of the day.

F. There is objective evidence from history, physical and neurological examination, or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in criteria A—D).

**Comments**

Emotional disturbances such as depression, anxiety or fear, irritability, euphoria, apathy, or wondering perplexity, disturbances of perception (illusions or hallucinations, often visual), and transient delusions are typical but are not specific indications for the diagnosis. A fourth character may be used to indicate whether or not the delirium is superimposed on dementia:

Delirium, not superimposed on dementia.

Delirium, superimposed on dementia

Other delirium

Delirium, unspecified

Other delirium

Delirium, unspecified

Reprinted with permission from World Health Organization: *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research.* © World Health Organization, Geneva, 1993.

**Table 10-27** Causes of Dementia

**Tumor**
- Primary cerebral*
- Metastatic*

**Trauma**
- Hematomas*
- Posttraumatic dementia*

**Infection (chronic)**
- Syphilis*
- Creutzfeldt-Jakob disease†
- AIDS dementia complex‡

**Cardiac/vascular**
- Single infarction*
- Multiple infarction†
- Large infarction
- Lacunar infarction
- Binswanger's disease (subcortical arteriosclerotic encephalopathies)
- Hemodynamic type*

**Congenital/hereditary**
- Huntington's disease‡
- Metachromatic leukodystrophy‡

**Primary psychiatric**
- Pseudodementia‡

**Physiological**
- Epilepsy*
- Normal pressure hydrocephalus*

**Metabolic**
- Vitamin deficiencies*
- Chronic metabolic disturbances*
- Chronic anoxic states*
- Chronic endocrinopathies*

**Degenerative dementias**
- Alzheimer's disease†
- Pick's disease (dementias of frontal lobe type)†
- Parkinson's disease*
- Progressive supranuclear palsy‡
- Idiopathic cerebral ferrocalcinosis (Fahr's disease)‡
- Wilson's disease*

**Demyelinating**
- Multiple sclerosis‡

**Drugs and toxins**
- Alcohol*
- Heavy metals*

Multiple sclerosis*

**Drugs and toxins**

Alcohol*
Heavy metals*
Carbon monoxide poisoning*
Medications*
Irradiation*

---

* Variable or mixed pattern.
† Predominantly cortical pattern.
‡ Predominantly subcortical pattern.

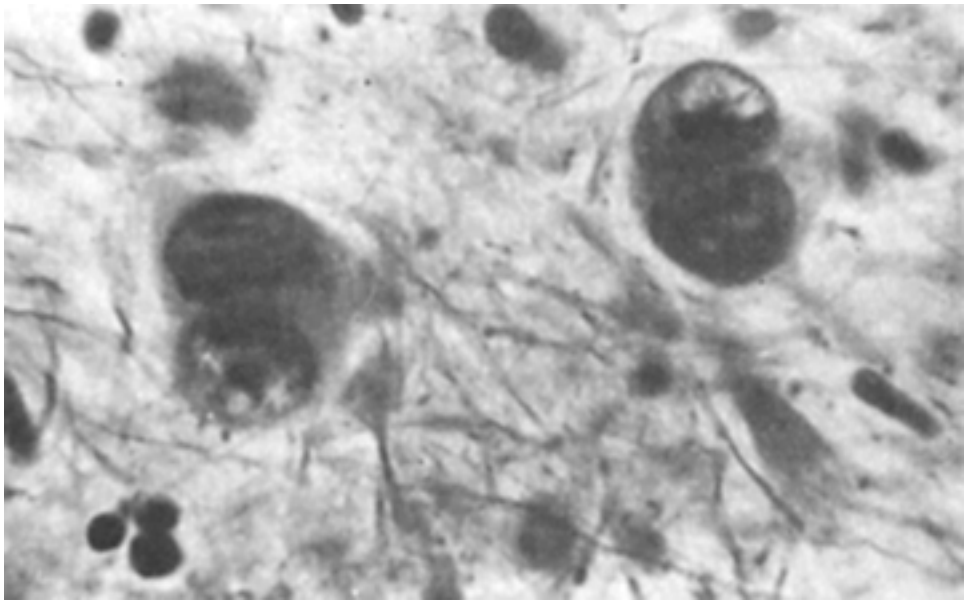

**FIGURE 10-12** Intraneuronal inclusions in Pick's disease. Silver stain. (Reprinted with permission from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, Baltimore, 1995.)

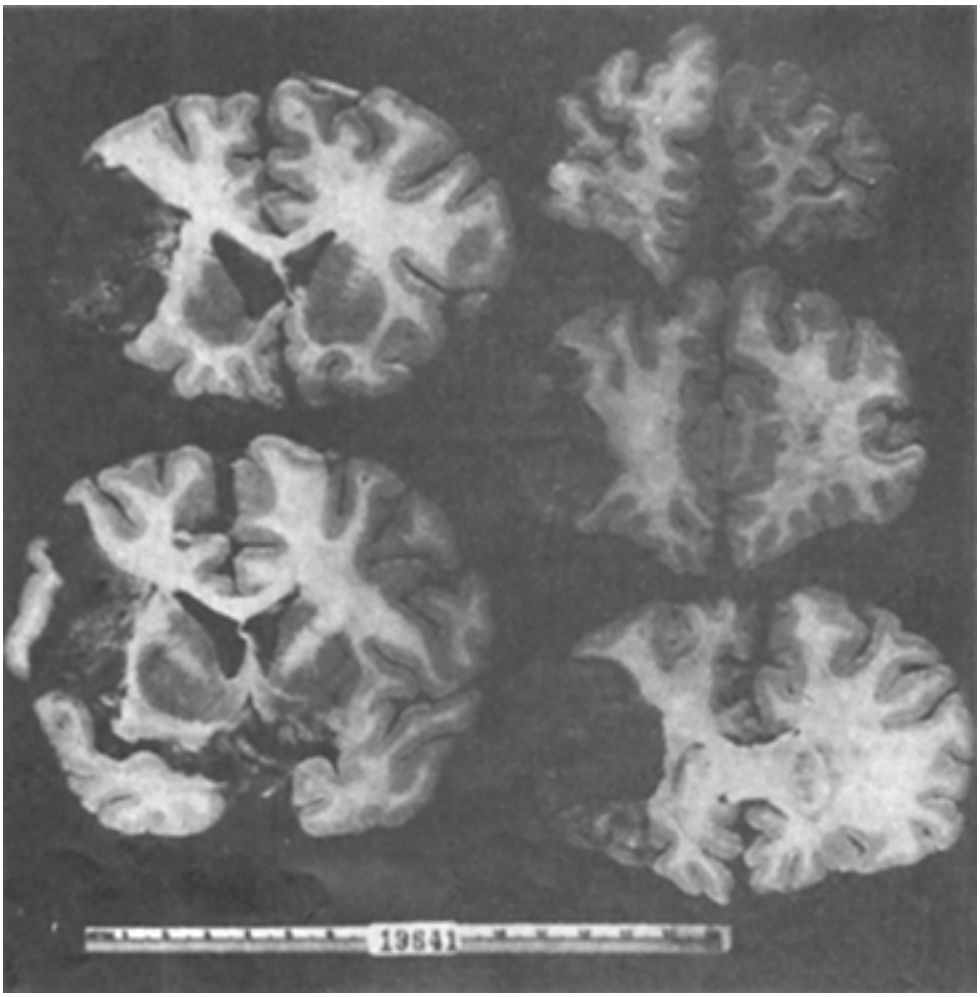


**FIGURE 10-13** Hemorrhagic infarct in the territory of the middle cerebral artery. (Reprinted with permission from Hirano A: *A Guide to Neuropathology*. Igaku-Shoin, New York, 1981.)

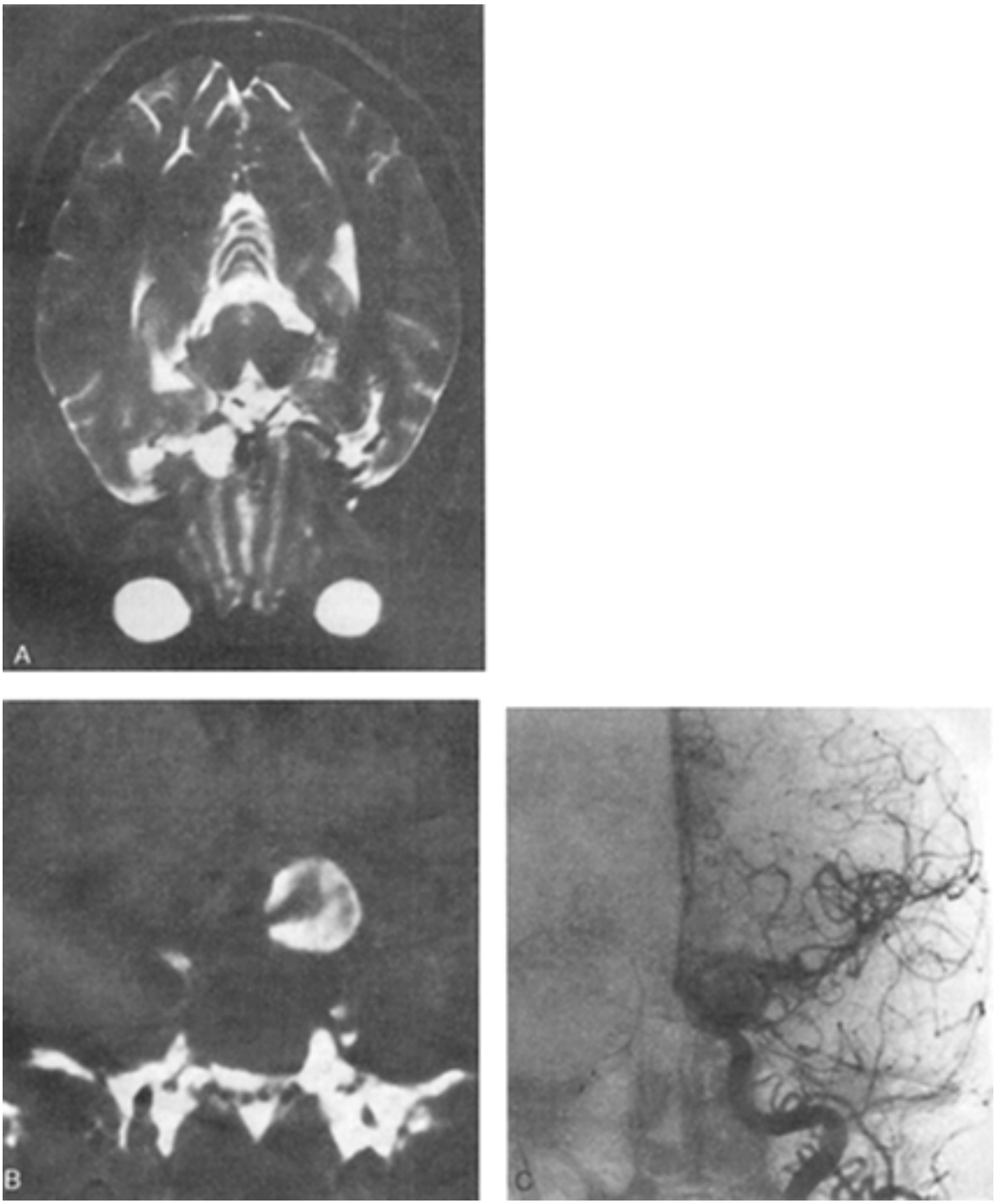


**FIGURE 10-14** Giant aneurysm. **A**, T2-weighted axial MRI scan shows a large, hyperintense mass in the left suprasellar region with medial displacement of the distal left internal carotid artery. **B**, T1-weighted coronal MRI scan demonstrates the heterogeneous parasellar mass; the areas of increased signal intensity indicate thrombus. A small curvilinear focus of flow void is seen medially most consistent with small residual patent vascular lumen. These findings are suggestive of partially thrombosed giant aneurysm. **C**, Anteroposterior view of arterial phase of left common carotid arteriogram illustrates a giant aneurysm of the left internal carotid artery. (Reprinted with permission

from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, Baltimore, 1995.)

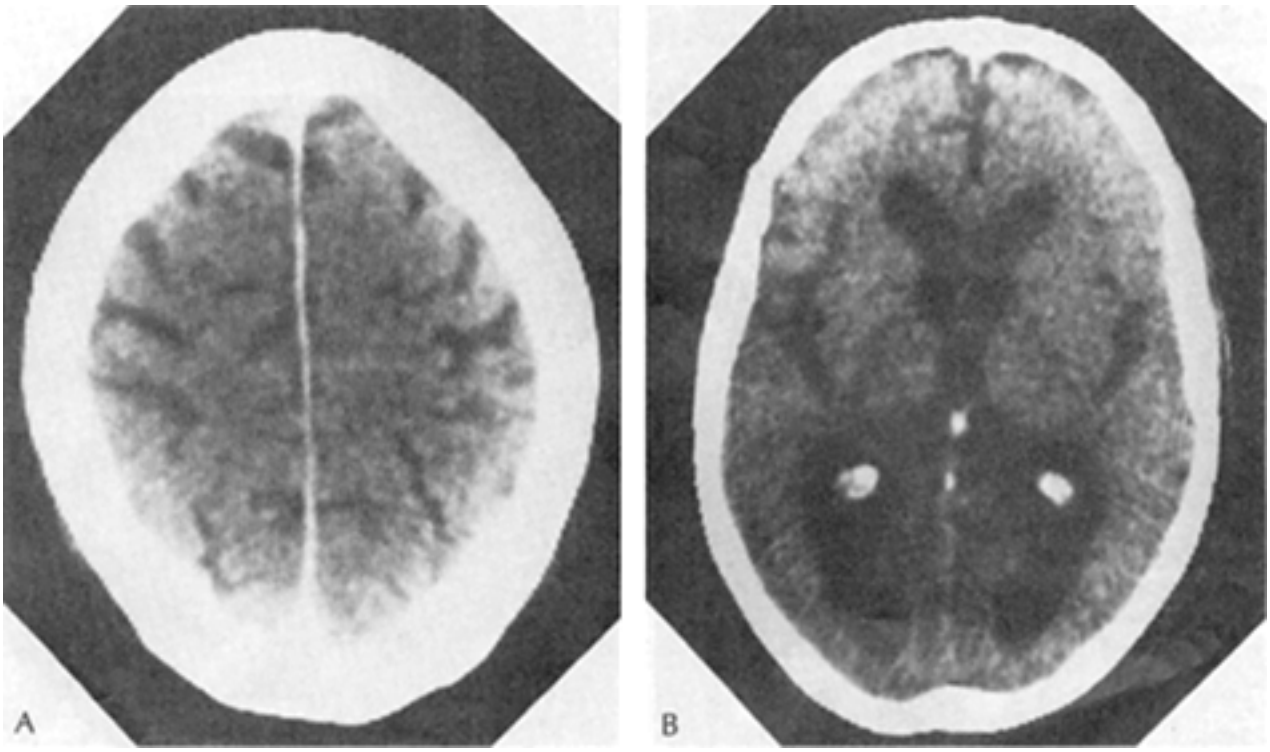


**FIGURE 10-15** Brain CT scans. Marked ventricular dilatation (**A**) and widening of cortical sulci (**B**) indicative of hydrocephalus ex vacuo in a 64-year-old woman with dementia. (Reprinted with permission from Rowland LP, editor: *Merritt's Textbook of Neurology*, ed 9. Williams & Wilkins, 1995.)

**Table 10-28** DSM-IV Diagnostic Criteria for Dementia of the Alzheimer's Type

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

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

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

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

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

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

*Code* based on type of onset and predominant features:
**With early onset:** if onset is at age 65 years or below
**With delirium:** if delirium is superimposed on the dementia
**With delusions:** if delusions are the predominant feature
**With depressed mood:** if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.
**Uncomplicated:** if none of the above predominates in the current clinical presentation
**With late onset:** if onset is after age 65 years
**With delirium:** if delirium is superimposed on the dementia

**Uncomplicated:** if none of the above predominates in the current clinical presentation

**With late onset:** if onset is after age 65 years

**With delirium:** if delirium is superimposed on the dementia

**With delusions:** if delusions are the predominant feature

**With depressed mood:** if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.

**Uncomplicated:** if none of the above predominates in the current clinical presentation

*Specify* if:

**With behavioral disturbance**

**Coding note:** Also code Alzheimer's disease on Axis III.

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**Table 10-29** DSM-IV Diagnostic Criteria for Vascular Dementia

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

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

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

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

*Code* based on predominant features:
**With delirium:** if delirium is superimposed on the dementia
**With delusions:** if delusions are the predominant feature
**With depressed mood:** if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.
**Uncomplicated:** if none of the above predominates in the current clinical presentation

*Specify* if:
**With behavioral disturbance**
**Coding note:** Also code cerebrovascular condition on Axis III.

**Table 10-30** DSM-IV Diagnostic Criteria for Dementia Due to Other General Medical Conditions

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

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

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of one of the general medical conditions listed below.

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

**Dementia due to HIV disease**

**Coding note:** Also code HIV infection on Axis III.

**Dementia due to head trauma**

**Coding note:** Also code head injury on Axis III.

**Dementia due to Parkinson's disease**

**Coding note:** Also code Parkinson's disease on Axis III.

**Dementia due to Huntington's disease**

**Coding note:** Also code Huntington's disease on Axis III.

**Dementia due to Pick's disease**

**Coding note:** Also code Pick's disease on Axis III.

**Dementia due to Creutzfeldt-Jakob disease**

**Coding note:** Also code Creutzfeldt-Jakob disease on Axis III.

**Dementia due to . . . [indicate the general medical condition not listed above]**

For example, normal pressure hydrocephalus, hypothyroidism, brain tumor, vitamin $B_{12}$ deficiency intracranial radiation

**Coding note:** Also code the general medical condition on Axis III.

brain tumor, vitamin $B_{12}$ deficiency intracranial radiation

**Coding note:** Also code the general medical condition on Axis III.

**Table 10-31** DSM-IV Diagnostic Criteria for Substance-Induced Persisting Dementia

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

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

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

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

*Code:* (Specific substance)-induced persisting dementia: (Alcohol; inhalant; sedative, hypnotic, or anxiolytic; other [or unknown] substance)

**Table 10-32** DSM-IV Diagnostic Criteria for Dementia Due to Multiple Etiologies

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

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

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

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

**Coding note:** Use multiple codes based on specific dementias and specific etiologies, e.g., dementia of the Alzheimer's type, with late onset uncomplicated; vascular dementia, uncomplicated.

**Table 10-33** DSM-IV Diagnostic Criteria for Dementia Not Otherwise Specified

| |
|---|
| This category should be used to diagnose a dementia that does not meet criteria for any of the specific types described in this section. An example is a clinical presentation of dementia for which there is insufficient evidence to establish a specific etiology. |

**Table 10-34** ICD-10 Diagnostic Criteria for Dementia

G1. There is evidence of each of the following:

(1) A decline in memory, which is most evident in the learning of new information, although, in more severe cases, the recall of previously learned information may also be affected. The impairment applies to both verbal and nonverbal material. The decline should be objectively verified by obtaining a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments. The severity of the decline, with mild impairment as the threshold for diagnosis, should be assessed as follows:

*Mild.* The degree of memory loss is sufficient to interfere with everyday activities, though not so severe as to be incompatible with independent living. The main function affected is the learning of new material. For example, the individual has difficulty in registering, storing, and recalling elements involved in daily living, such as where belongings have been put, social arrangements, or information recently imparted by family members.

*Moderate.* The degree of memory loss represents a serious handicap to independent living. Only highly learned or very familiar material is retained. New information is retained only occasionally and very briefly. Individuals are unable to recall basic information about their own local geography, what they have recently been doing, or the names of familiar people.

*Severe.* The degree of memory loss is characterized by the complete inability to retain new information. Only fragments of previously learned information remain. The individual fails to recognize even close relatives.

(2) A decline in other cognitive abilities characterized by deterioration in judgment and thinking, such as planning and organizing, and in the general processing of information. Evidence for this should ideally be obtained from an informant and supplemented, if possible, by neuropsychological tests or quantified objective assessments. Deterioration from a previously higher level of performance should be established. The severity of the decline, with mild impairment as the threshold for diagnosis, should be assessed as follows:

*Mild.* The decline in cognitive abilities causes impaired performance in daily living, but not to a degree that makes the individual dependent on others. Complicated daily tasks or recreational activities cannot be undertaken.

*Moderate.* The decline in cognitive abilities makes the individual unable to function without the assistance of another in daily living, including shopping and handling money. Within the home, only simple chores can be performed. Activities are increasingly restricted and poorly sustained.

*Severe.* The decline is characterized by an absence, or virtual absence, of intelligible ideation.

The overall severity of the dementia is best expressed as the level of decline in memory or other cognitive abilities, whichever is the more severe (e.g., mild decline in memory *and* moderate decline in cognitive abilities indicate a dementia of moderate severity).

G2. Awareness of the environment (i.e., absence of clouding of consciousness [as defined in delirium, not induced by alcohol and other psychoactive substances, criterion A]) is preserved during a period sufficiently long to allow the unequivocal demonstration of the symptoms in criterion G1. When there are superimposed episodes of delirium, the diagnosis of dementia should be deferred.

G3. There is a decline in emotional control or motivation, or a change in social behavior manifest as at least one of the following:
(1) emotional lability
(2) irritability
(3) apathy
(4) coarsening of social behavior

G4. For a confident clinical diagnosis, the symptoms in criterion G1 should have been present for at least 6 months; if the period since the manifest onset is shorter, the diagnosis can be only tentative.

***Comments***

The diagnosis is further supported by evidence of damage to other higher cortical functions, such as aphasia, agnosia, apraxia.

Judgment about independent living or the development of dependence (upon others) should take account of the cultural expectation and context.

Dementia is specified here as having a minimum duration of 6 months to avoid confusion with reversible states with identical behavioral syndromes, such as traumatic subdural hemorrhage, normal pressure hydrocephalus and diffuse or focal brain injury.

A fifth character may be used to indicate the presence of additional symptoms: Dementia in Alzheimer's disease, vascular dementia, dementia in diseases classified elsewhere, unspecified dementia, as follows:
Without additional symptoms
With other symptoms, predominantly delusional
With other symptoms, predominantly hallucinatory
With other symptoms, predominantly depressive
With other mixed symptoms

A sixth character may be used to indicate the severity of the dementia:
Mild
Moderate
Severe

As mentioned above, the overall severity of the dementia depends on the level of memory or intellectual impairment whichever is the more severe.

**Table 10-35** ICD-10 Diagnostic Criteria for Dementia in Alzheimer's Disease

A. The general criteria for dementia G1–G4 must be met.

B. There is no evidence from the history, physical examination, or special investigations for any other possible cause of dementia (e.g., cerebrovascular disease, HIV disease, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus), a systemic disorder (e.g., hypothyroidism, vitamin $B_{12}$, or folic acid deficiency, hypercalcemia), or alcohol or drug abuse.

Comments

The diagnosis is confirmed by postmortem evidence of neurofibrillary tangles and neuritic plaques in excess of those found in normal aging of the brain.

The following features support the diagnosis, but are not necessary elements: involvement of cortical functions as evidenced by aphasia, agnosia or apraxia; decrease of motivation and drive, leading to apathy and lack of spontaneity; irritability and disinhibition of social behavior; evidence from special investigations that there is cerebral atrophy, particularly if this can be shown to be increasing over time. In severe cases there may be Parkinson-like extrapyramidal changes, logoclonia, and epileptic fits.

Specification of features for possible subtypes

Because of the possibility that subtypes exist, it is recommended that the following characteristics be ascertained as a basis for a further classification: age at onset; rate of progression; configuration of the clinical features, particularly the relative prominence (or lack) of temporal parietal, or frontal lobe signs; any neuropathological or neurochemical abnormalities, and their pattern.

The division of Alzheimer's disease into subtypes can at present be accomplished in two ways: first by taking only the age of onset and labeling the disease as either early or late, with an approximate cut-off point at 65 years; or second, by assessing how well the individual conforms to one of the two putative syndromes early or late-onset type.

It should be noted that a sharp distinction between early- and late-onset types is unlikely. Early-onset type may occur in late life, just as late-onset type may occasionally have an onset before the age of 65. The following criteria may be used to differentiate dementia in Alzheimer's disease with early and late onset, but it should be remembered that the status of this subdivision is still controversial.

Dementia in Alzheimer's diseases with early onset

1. The criteria for dementia in Alzheimer's disease must be met, and the age at onset must be below 65 years.
2. In addition, at least one of the following requirements must be met:
   (a) evidence of a relatively rapid onset and progression;
   (b) in addition to memory impairment, there must be aphasia

and the age at onset must be below 65 years.

2. In addition, at least one of the following requirements must be met:
   (a) evidence of a relatively rapid onset and progression;
   (b) in addition to memory impairment, there must be aphasia (amnesic or sensory), agraphia, alexia, acalculia, or apraxia (indicating the presence of temporal, parietal, and/or frontal lobe involvement).

Dementia in Alzheimer's disease with late onset

1. The criteria for dementia in Alzheimer's disease must be met and the age at onset must be 65 years or more.
2. In addition, at least one of the following requirements must be met:
   (a) evidence of a very slow, gradual onset and progression (the rate of the latter may be known only retrospectively after a course of 3 years or more);
   (b) predominance of memory impairment G1(1), over intellectual impairment G1(2) (see general criteria for dementia).

Dementia in Alzheimer's disease, atypical or mixed type

This term and code should be used for dementias that have important atypical features or that fulfill criteria for both early- and late-onset types of Alzheimer's disease. Mixed Alzheimer's and vascular dementia are also included here.

Dementia in Alzheimer's disease, unspecified

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**Table 10-36** ICD-10 Diagnostic Criteria for Vascular Dementia

G1. The general criteria for dementia (G1–G4) must be met.

G2. Deficits in higher cognitive functions are unevenly distributed, with some functions affected and others relatively spared. Thus, memory may be markedly affected while thinking, reasoning, and information processing may show only mild decline.

G3. There is clinical evidence of focal brain damage, manifest as at least one of the following:
(1) unilateral spastic weakness of the limbs;
(2) unilaterally increased tendon reflexes;
(3) extensor plantar response;
(4) pseudobulbar palsy.

G4. There is evidence from the history, examination, or tests of a significant cerebrovascular disease, which may reasonably be judged to be etiologically related to the dementia (e.g., a history of stroke, evidence of cerebral infarction).

The following criteria may be used to differentiate subtypes of vascular dementia, but it should be remembered that the usefulness of this subdivision may not be generally accepted.

**Vascular dementia of acute onset**

A. The general criteria for vascular dementia must be met.
B. The dementia develops rapidly (i.e., usually within 1 month, but within no longer than 3 months) after a succession of strokes or (rarely) after a single large infarction.

**Multi-infarct dementia**

A. The general criteria for vascular dementia must be met.
B. The onset of the dementia is gradual (i.e., within 3–6 months), following a number of minor ischemic episodes.

**Comments**

It is presumed that there is an accumulation of infarcts in the cerebral parenchyma. Between the ischemic episodes there may be periods of actual clinical improvement.

**Subcortical vascular dementia**

A. The general criteria for vascular dementia must be met.
B. There is a history of hypertension.
C. There is evidence from clinical examination and special investigations of vascular disease located in the deep white matter of the cerebral hemispheres, with preservation of the cerebral cortex.

**Mixed cortical and subcortical vascular dementia**

Mixed cortical and subcortical components of the vascular dementia may be suspected from the clinical features, the results of investiga-

cortex.

**Mixed cortical and subcortical vascular dementia**

Mixed cortical and subcortical components of the vascular dementia may be suspected from the clinical features, the results of investigations (including autopsy), or both.

**Other vascular dementia**

**Vascular dementia unspecified**

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**Table 10-37** ICD-10 Diagnostic Criteria for Dementia in Other Diseases Classified Elsewhere

Dementia in Pick's disease

A. The general criteria for dementia (G1–G4) must be met.
B. Onset is slow with steady deterioration.
C. Predominance of frontal lobe involvement is evidenced by two or more of the following:
   (1) emotional blunting;
   (2) coarsening of social behavior;
   (3) disinhibition;
   (4) apathy or restlessness;
   (5) aphasia.
D. In the early stages, memory and parietal lobe functions are relatively preserved.

Dementia in Creutzfeldt-Jakob disease

A. The general criteria for dementia (G1–G4) must be met.
B. There is very rapid progression of the dementia, with disintegration of virtually all higher cerebral functions.
C. One or more of the following types of neurological symptoms and signs emerge, usually after or simultaneously with the dementia:
   (1) pyramidal symptoms;
   (2) extrapyramidal symptoms;
   (3) cerebellar symptoms;
   (4) aphasia;
   (5) visual impairment.

Comments

An akinetic and mute state is the typical terminal stage. An amyotrophic variant may be seen, where the neurological signs precede the onset of the dementia. A characteristic electroencephalogram (periodic spikes against a slow and low-voltage background), if present in association with the above clinical signs, increases the probability of the diagnosis. However, the diagnosis can be confirmed only by neuropathological examination (neuronal loss, astrocytosis, and spongiform changes). Because of the risk of infection, this should be carried out only under special protective conditions.

Dementia in Huntington's disease

A. The general criteria for dementia (G1–G4) must be met.
B. Subcortical functions are affected first and dominate the picture of dementia throughout; subcortical involvement is manifested by slowness of thinking or movement and personality alteration with apathy or depression.
C. There are involuntary choreiform movements, typically of the face, hands, or shoulders, or the gait. The patient may attempt to conceal them by converting them into a voluntary action.
D. There is a history of Huntington's disease in one parent or a sibling, or a family history that suggests the disorder.
E. There are no clinical features that otherwise account for the abnormal movements.

Comments

In addition to involuntary choreiform movements, there may be development of extrapyramidal rigidity or of spasticity with pyramidal signs.

Dementia in Parkinson's disease

A. The general criteria for dementia (G1–G4) must be met.
B. A diagnosis of Parkinson's disease has been established.
C. None of the cognitive impairment is attributable to anti-parkinsonian medication.
D. There is no evidence from the history, physical examination, or special investigations for any other possible cause of dementia, including other forms of brain disease, damage, or dysfunction (e.g., cerebrovascular disease, HIV disease, Huntington's disease, normal pressure hydrocephalus), a systemic disorder (e.g., hypothyroidism, vitamin $B_{12}$ or folic acid deficiency, hypercalcemia), or alcohol or drug abuse.

If criteria are also fulfilled for dementia in Alzheimer's disease with late onset, that category should be used in combination with Parkinson's disease.

Dementia in human immunodeficiency virus (HIV) disease

A. The general criteria for dementia (G1–G4) must be met.
B. A diagnosis of HIV infection has been established.
C. There is no evidence from the history, physical examination, or special investigations for any other possible cause of dementia, including other forms of brain disease, damage, or dysfunction (e.g., Alzheimer's disease, cerebrovascular disease, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus), a systemic disorder (e.g., hypothyroidism, vitamin $B_{12}$ or folic acid deficiency, hypercalcemia), or alcohol or drug abuse.

Dementia in other specified diseases classified elsewhere

Dementia can occur as a manifestation or consequence of a variety of cerebral and somatic conditions. To specify the etiology, the ICD-10 code for the underlying condition should be added.

**Table 10-38** DSM-IV Diagnostic Criteria for Amnestic Disorder Due to a General Medical Condition

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

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

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

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

*Specify if:*

**Transient:** if memory impairment lasts for 1 month or less

**Chronic:** if memory impairment lasts for more than 1 month

**Coding note:** Include the name of the general medical condition on Axis I, e.g., amnestic disorder due to head trauma; also code the general medical condition on Axis III.

**Table 10-39** DSM-IV Diagnostic Criteria for Substance-Induced Persisting Amnestic Disorder

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

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

C. The memory disturbance does not occur exclusively during the course of a delirium or a dementia and persists beyond the usual duration of substance intoxication or withdrawal.

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

*Code:* (Specific substance)-induced persisting amnestic disorder: (Alcohol; sedative, hypnotic, or anxiolytic; other [or unknown] substance)

**Table 10-40** DSM-IV Amnestic Disorder Not Otherwise Specified

| |
|---|
| This category should be used to diagnose an amnestic disorder that does not meet criteria for any of the specific types described in this section. |
| An example is a clinical presentation of amnesia for which there is insufficient evidence to establish a specific etiology (i.e., dissociative, substance induced, or due to a general medical condition). |

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**Table 10-41** ICD-10 Diagnostic Criteria for Organic Amnesic Syndrome, Not Induced by Alcohol and Other Psychoactive Substances

A. There is memory impairment, manifest in both
   1. A defect of recent memory (impaired learning of new material) to a degree sufficient to interfere with daily living
   2. A reduced ability to recall past experiences

B. There is no
   1. Defect in immediate recall (as tested, for example, by the digit span)
   2. Clouding of consciousness and disturbance of attention. Delirium, not induced by alcohol and other psychoactive substances
   3. Global intellectual decline (dementia)

C. There is objective evidence (from physical and neurological examination, laboratory tests) and/or history of an insult to, or a disease of the brain (especially, involving bilaterally the diencephalic and medial temporal structures but other than alcohol encephalopathy) that can reasonably be presumed to be responsible for the clinical manifestations

*Comments:* Associated features, including confabulations, emotional changes (apathy, lack of initiative), and lack of insight are useful additional pointers to the diagnosis but are not invariably present.

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**Table 10-42** DSM-IV Diagnostic Criteria for Cognitive Disorder Not Otherwise Specified

This category is for disorders that are characterized by cognitive dysfunction presumed to be due to the direct physiological effects of a general medical condition that do not meet criteria for any of the specific deliriums, dementias, or amnestic disorders listed in this section and that are not better classified as delirium not otherwise specified, dementia not otherwise specified, or amnestic disorder not otherwise specified. For cognitive dysfunction due to a specific or unknown substance, the specific substance-related disorder not otherwise specified category should be used.

Examples include

1. Mild neurocognitive disorder: impairment in cognitive functioning as evidenced by neuropsychological testing or quantified clinical assessment accompanied by objective evidence of a systemic general medical condition of central nervous system dysfunction.
2. Postconcussional disorder: following a head trauma, impairment in memory or attention with associated symptoms.

**Table 10-43** ICD-10 Diagnostic Criteria for Other Mental Disorders Due to Brain Damage and Dysfunction and Due to Physical Disease

G1. There is objective evidence (from physical and neurological examination and laboratory tests) and/or history of cerebral disease, damage, or dysfunction, or of systemic physical disorder known to cause cerebral dysfunction, including hormonal disturbances (other than alcohol- or other psychoactive substance-related) and nonpsychoactive drug effects.

G2. There is a presumed relationship between the development (or marked exacerbation) of the underlying disease, damage, or dysfunction, and the mental disorder, the symptoms of which may have immediate onset or may be delayed.

G3. There is recovery from or significant improvement in the mental disorder following removal or improvement of the underlying presumed cause.

G4. There is insufficient evidence for an alternative causation of the mental disorder, e.g., a strong family history of a clinically similar or related disorder.

If criteria G1, G2, and G4 are met, a provisional diagnosis is justified; if, in addition, there is evidence of G3, the diagnosis can be regarded as certain.

**Organic hallucinosis**

A. The general criteria for other mental disorders due to brain damage and dysfunction and to physical disease must be met.

B. The clinical picture is dominated by persistent or recurrent hallucinations (usually visual or auditory).

C. Hallucinations occur in clear consciousness.

*Comments*

Delusional elaboration of the hallucinations, as well as full or partial insight, may or may not be present: these features are not essential for the diagnosis.

**Organic catatonic disorder**

A. The general criteria for other mental disorders due to brain damage and dysfunction and to physical disease must be met.

B. One of the following must be present:
(1) Stupor, ie, profound diminution or absence of voluntary movements and speech, and of normal responsiveness to light, noise, and touch, but with normal muscle tone, static posture, and breathing maintained (and often limited coordinated eye movements);
(2) negativism (positive resistance to passive movement of limbs or body or rigid posturing).

C. There is catatonic excitement (gross hypermotility of a chaotic quality, with or without a tendency to assaultiveness).

D. There is rapid and unpredictable alternation of stupor and excitement.

*Comments*

Confidence in the diagnosis is increased if additional catatonic phenomena are present, e.g., stereotypies, waxy flexibility, and impulsive acts. Care should be taken to exclude delirium; however, it is not known whether an organic catatonic state always occurs in clear consciousness, or whether it represents an atypical manifestation of a delirium in which criteria A, B, and D are only marginally met, whereas criterion C is prominent.

**Organic delusional (schizophrenia-like) disorder**

A. The general criteria for other mental disorders due to brain damage and dysfunction and to physical disease must be met.

B. The clinical picture is dominated by delusions (of persecution, bodily change, disease, death, jealousy), which may exhibit a varying degree of systematization.

C. Consciousness is clear and memory is intact.

*Comments*

Further features that complete the clinical picture but that are not invariably present include: hallucinations (in any modality); schizophrenic-type thought disorder; isolated catatonic phenomena such as stereotypies, negativism, or impulsive acts.

The clinical picture may meet the symptomatic criteria for schizophrenia, persistent delusional disorder, or acute and transient psychotic disorders. However, if the state also meets the general criteria for a presumptive organic etiology laid down in the introduction to other mental disorders due to brain damage and dysfunction and to physical disease, it should be classified here. Marginal or nonspecific findings such as enlarged cerebral ventricles or "soft" neurological signs *do not qualify as evidence* for criterion G1 of other mental disorders due to brain damage and dysfunction and to physical disease.

The diagnosis of the affective disorder may be specified by using a fifth character:
**Organic manic disorder**
**Organic bipolar disorder**
**Organic depressive disorder**
**Organic mixed affective disorder**
**Organic anxiety disorder**

A. The general criteria for other medical disorders due to brain damage and dysfunction and to physical disease must be met.

B. The condition must meet the criteria for either panic disorder or generalized anxiety disorder.

**Organic dissociative disorder**

A. The general criteria for other mental disorders due to brain damage and dysfunction and to physical disease must be met.

B. The condition must meet the criteria for one of the dissociative (conversion) disorders categories.

**Organic emotionally labile (asthenic) disorder**

A. The general criteria for other mental disorders due to brain damage and dysfunction and to physical disease must be met.

B. The clinical picture is dominated by emotional lability (uncontrolled, unstable, and fluctuating expression of emotions).

C. There is a variety of unpleasant physical sensations such as dizziness or pains and aches.

*Comments*

Fatigability and listlessness (asthenia) are often present but are not essential for the diagnosis.

Mild cognitive disorder

*Note:* The status of this construct is being examined. Specific research criteria must be viewed as tentative. One of the principal reasons for its inclusion is to obtain further evidence, allowing its differentiation from disorders such as dementia, organic amnestic syndrome, delirium, and several disorders in personality and behavioral disorders due to brain disease, damage, and dysfunction.

A. The general criteria for other mental disorders due to brain damage and dysfunction and to physical disease must be met.

B. There is a disorder in cognitive function for most of the time over a period of at least 2 weeks, as reported by the individual or a reliable informant. The disorder is exemplified by difficulties in any of the following areas:
(1) memory (particularly recall) or new learning;
(2) attention or concentration;
(3) thinking (e.g., slowing in problem solving or abstraction);
(4) language (e.g., comprehension, word finding);
(5) visual-spatial functioning.

C. There is an abnormality or decline in performance in quantified cognitive assessments (e.g., neuropsychological tests or mental status examination).

D. None of the difficulties listed in criterion B (1)–(5) is such that a diagnosis made of dementia, organic amnesic syndrome, delirium, postencephalitic syndrome, postconcussional syndrome, or other persisting cognitive impairment due to psychoactive substance use.

*Comments*

If criterion G1 for other mental disorders due to brain damage and dysfunction and to physical disease is fulfilled by the presence of central nervous system dysfunction, it is usually presumed that this is the cause of the mild cognitive disorder. If criterion G1 is fulfilled by the presence of a systemic physical disorder, it is often unjustified to assume that there is a direct causative relationship. Nevertheless, it may be useful in such instances to record the presence of the systemic physical disorder as "associated," without implying a necessary causation. An additional fifth character may be used for this:

**Not associated with a systemic physical disorder**

**Associated with a systemic physical disorder**

The systemic physical disorder should be recorded separately by its appropriate ICD-10 code.

**Other specified mental disorders due to brain damage and dysfunction and to physical disease**

Examples of this category are transient or mild abnormal mood states occurring during treatment with steroids or antidepressants which do not meet the criteria

laid down in the introduction to other mental disorders due to brain damage and dysfunction and to physical disease, it should be classified here. Marginal or nonspecific findings such as enlarged cerebral ventricles or "soft" neurological signs *do not qualify as evidence* for criterion G1 of other mental disorders due to brain damage and dysfunction and to physical disease.

**Organic mood (affective) disorder**

A. The general criteria for other medical disorders due to brain damage and dysfunction and to physical disease must be met.

B. The condition must meet the criteria for one of the affective disorders.

ICD-10 code.

**Other specified mental disorders due to brain damage and dysfunction and to physical disease**

Examples of this category are transient or mild abnormal mood states occurring during treatment with steroids or antidepressants which do not meet the criteria for organic mood disorder.

**Unspecified mental disorder due to brain damage and dysfunction and to physical disease**

**Table 10-44** DSM-IV Research Criteria for Mild Neurocognitive Disorder

A. The presence of two (or more) of the following impairments in cognitive functioning, lasting most of the time for a period of at least 2 weeks (as reported by the individual or a reliable informant):
   (1) memory impairment as identified by a reduced ability to learn or recall information
   (2) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
   (3) disturbance in attention or speed of information processing
   (4) impairment in perceptual-motor abilities
   (5) impairment in language (e.g., comprehension, word finding)

B. There is objective evidence from physical examination or laboratory findings (including neuroimaging techniques) of a neurological or general medical condition that is judged to be etiologically related to the cognitive disturbance.

C. There is evidence from neuropsychological testing or quantified cognitive assessment of an abnormality or decline in performance.

D. The cognitive deficits cause marked distress or impairment in social, occupational, or other important areas of functioning and represent a decline from a previous level of functioning.

E. The cognitive disturbance does not meet criteria for a delirium, a dementia, or an amnestic disorder and is not better accounted for by another mental disorder (e.g., a substance-related disorder, major depressive disorder).

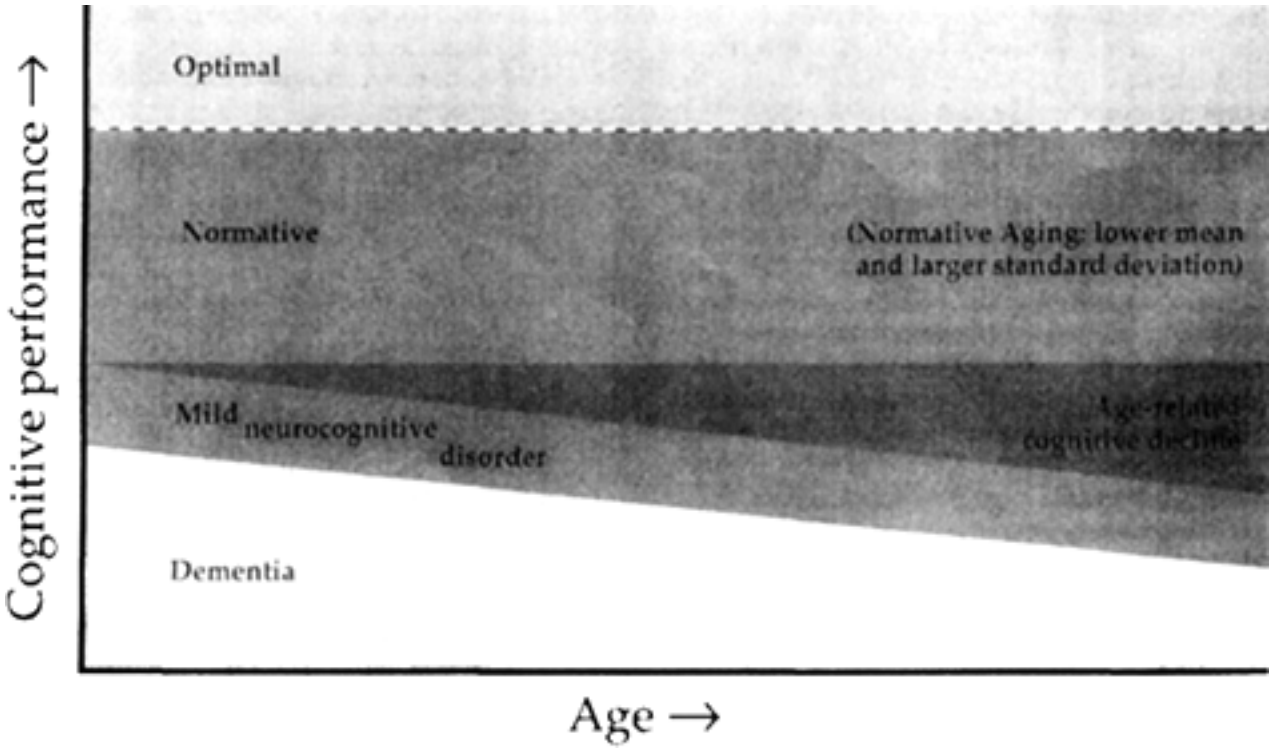


**FIGURE 10-16** Aging-associated changes in ranges of cognitive performance.

**Table 10-45** Mental Disorders Due to a General Medical Condition

| DSM-IV Category | Mental Disorders due to a General Medical Condition |
|---|---|
| Delirium, dementia, amnestic, and other cognitive disorders | Delirium due to a general medical condition<br>Dementia due to other general medical conditions<br>Amnestic disorder due to a general medical condition |
| Schizophrenia and other psychotic disorders | Psychotic disorder due to a general medical condition |
| Mood disorders | Mood disorder due to a general medical condition |
| Anxiety disorders | Anxiety disorder due to a general medical condition |
| Sexual disorders | Sexual dysfunction due to a general medical condition |
| Sleep disorders | Sleep disorder due to a general medical condition |
| Mental disorders due to a general medical condition not elsewhere classified | Catatonic disorder due to a general medical condition<br>Personality change due to a general medical condition<br>Mental disorder not otherwise specified due to a general medical condition |

**Table 10-46** Causes of Secondary Mood Disorders

| |
|---|
| **Drug intoxication** |
| Alcohol or sedative-hypnotics (as examples) |
| Antipsychotics |
| Antidepressants |
| Metoclopramide, $H_2$-receptor blockers |
| Antihypertensives (especially centrally acting agents, e.g., methyldopa, clonidine, reserpine) |
| Sex steroids (e.g., oral contraceptives, anabolic steroids) |
| Glucocorticoids |
| Levodopa |
| Bromocriptine |
| **Drug withdrawal** |
| Nicotine, caffeine, alcohol or sedative-hypnotics, cocaine, amphetamines |
| **Tumor** |
| Primary cerebral |
| Systemic neoplasm |
| **Trauma** |
| Cerebral contusion |
| Subdural hematoma |
| **Infection** |
| Cerebral (e.g., meningitis, encephalitis, HIV, syphilis) |
| Systemic (e.g., sepsis, urinary tract infection, pneumonia) |
| **Cardiac and vascular** |
| Cerebrovascular (e.g., infarcts, hemorrhage, vasculitis) |
| Cardiovascular (e.g., low-output states, congestive heart failure, shock) |
| **Physiological or metabolic** |
| Hypoxemia, electrolyte disturbances, renal or hepatic failure, hypo- or hyperglycemia, postictal states |
| **Endocrine** |
| Thyroid or glucocorticoid disturbances |
| **Nutritional** |
| Vitamin $B_{12}$, (?)folate deficiency |
| **Demyelinating** |
| Multiple sclerosis |
| **Neurodegenerative** |
| Parkinson's disease, Huntington's disease |

**Table 10-47** Psychotic Symptoms Associated With Abnormality of Specific Brain Regions

| Symptoms | Site | Laterality |
|---|---|---|
| First-rank symptoms<br>Thoughts spoken aloud<br>Voices commenting<br>Third-person voices arguing<br>Made actions<br>Made feelings<br>Thought withdrawal<br>Thought diffusion<br>Delusional perception | Temporal lobe | Dominant hemisphere |
| Complex delusions | Subcortical or limbic | |
| Anton syndrome | Occipital lobe, optic tract | Bilateral |
| Anosognosia | Parietal lobe | Nondominant hemisphere |
| Misidentification syndromes<br>Capgras syndrome<br>Reduplicative paramnesia<br>Fregoli syndrome<br>Intermetamorphosis syndrome | Parietal, temporal, frontal lobes | Nondominant hemisphere, bilateral |

**Table 10-48** Medical Conditions Commonly Associated With a Secondary Sleep Disorder

| Condition | Sleep Symptoms |
|---|---|
| Parkinsonism | Frequent awakenings, disturbance of circadian rhythms |
| Dementia | Sundowning, frequent awakenings |
| Epilepsy | Difficulty initiating sleep, frequent awakenings, parasomnias |
| Cerebrovascular disease | Difficulty initiating sleep, frequent awakenings |
| Huntington's disease | Frequent awakening |
| Kleine-Levin syndrome | Hypersomnia |
| Uremia | Restless legs, nocturnal myoclonus |

**Table 10-49** Causes of Secondary Sexual Dysfunctions

| |
|---|
| **Medications** |
| Cardiac drugs, antihypertensives (e.g., reserpine, β-adrenergic receptor antagonists clonidine, α-methyldopa, diuretics) |
| $H_2$-receptor blockers |
| Carbonic anhydrase inhibitors |
| Anticholinergics |
| Anticonvulsants (e.g., carbamazepine, phenytoin, primidone) |
| Antipsychotics |
| Antidepressants (e.g., tricyclics, MAO oxidase inhibitors, trazodone, SSRIs) |
| Sedative-hypnotics |
| **Substances of abuse** |
| Alcohol |
| Opioids |
| Stimulants |
| Cannabis |
| Sedative-hypnotics |
| **Local disease processes that affect primary or secondary sexual organs** |
| Congenital anomalies or malformations |
| Trauma |
| Tumor |
| Infection |
| Postsurgical or postirradiation local neurological and vascular pathology |
| **Systemic disease processes** |
| Neurological |
| Central nervous system (e.g., strokes, multiple sclerosis) |
| Peripheral nervous system (e.g., peripheral neuropathy) |
| Vascular |
| Atherosclerosis, vasculitis (as examples) |
| Endocrine |
| Diabetes mellitus, alterations in function of thyroid, adrenal cortex, gonadotropins, gonadal hormones (as examples) |

**Table 10-50** DSM-IV Diagnostic Criteria for Catatonic Disorder Due to a General Medical Condition

A. The presence of catatonia as manifested by motoric immobility, excessive motor activity (that is apparently purposeless and not influenced by external stimuli), extreme negativism or mutism, peculiarities of voluntary movement, or echolalia or echopraxia.

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

C. The disturbance is not better accounted for by another mental disorder (e.g., a manic episode).

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

**Coding note:** Include the name of the general medical condition on Axis I, e.g., catatonic disorder due to hepatic encephalopathy; also code the general medical condition on Axis III.

**Table 10-51** DSM-IV Mental Disorder Not Otherwise Specified Due to a General Medical Condition

This residual category should be used for situations in which it has been established that the disturbance is caused by the direct physiological effects of a general medical condition, but the criteria are not met for a specific mental disorder due to a general medical condition (e.g., dissociative symptoms due to a complex partial seizure).

**Coding note:** Include the name of the general medical condition on Axis I, e.g., mental disorder not otherwise specified due to HIV disease; also code the general medical condition on Axis III.

**Table 10-52** DSM-IV Diagnostic Criteria for Personality Change Due to a General Medical Condition

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

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

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

D. The disturbance does not occur exclusively during the course of a delirium and does not meet criteria for a dementia.

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

*Specify type:*

**Labile type:** if the predominant feature is affective lability

**Disinhibited type:** if the predominant feature is poor impulse control as evidenced by sexual indiscretions, etc.

**Aggressive type:** if the predominant feature is aggressive behavior

**Apathetic type:** if the predominant feature is marked apathy and indifference

**Paranoid type:** if the predominant feature is suspiciousness or paranoid ideation

**Other type:** if the predominant feature is not one of the above, e.g., personality change associated with a seizure disorder.

**Combined type:** if more than one feature predominates in the clinical picture

**Unspecified type**

**Coding note:** include the name of the general medical condition on Axis I, e.g., personality change due to temporal lobe epilepsy, also code the general medical condition on Axis III.

Harold I. Kaplan, M.D, Benjamin J. Sadock, M.D and Virginia A. Sadock, M.D.
Kaplan & Sadock's Comprehensive Textbook of Psychiatry

**Table 10-53** Frontal Lobe Personality Change Syndromes

| Orbitofrontal | Frontopolar |
|---|---|
| Disinhibition | Apathy |
| Inappropriate jocularity | Indifference |
| Affective lability | Psychomotor slowing |
| Impulsivity | Inaction |


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