MEDICAL ASPECTS OF THE PERSISTENT VEGETATIVE STATE
(First of Two Parts)

THE Multi-Society Task Force on PVS*

Abstract This consensus statement of the Multi-Society Task Force summarizes current knowledge of the medical aspects of the persistent vegetative state in adults and children.

The vegetative state is a clinical condition of complete unawareness of the self and the environment, accompanied by sleep-wake cycles, with either complete or partial preservation of hypothalamic and brain-stem autonomic functions. In addition, patients in a vegetative state show no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; show no evidence of language comprehension, expression; have bowel and bladder incontinence; and have variably preserved cranial-nerve and spinal reflexes. We define persistent vegetative state as a vegetative state present one month after acute traumatic or nontraumatic brain injury or lasting for at least one month in patients with degenerative or metabolic disorders or developmental malformations.

The term "persistent vegetative state" was coined by Jennett and Plum in 1972 to describe the condition of patients with severe brain damage in whom coma has progressed to a state of wakefulness without detectable awareness. Such patients have sleep-wake cycles but no ascertainable cerebral cortical function. Jennett and Plum thought that patients in a persistent vegetative state could be distinguished clinically from those with other conditions associated with prolonged unconsciousness.

In 1983 the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research accepted the definition of persistent vegetative state proposed by Jennett and Plum and defined unconsciousness as the inability "to experience the environment." In the commission's judgment, a persistent vegetative state is only one form of permanent unconsciousness. The others include coma after a traumatic or nontraumatic injury, with death occurring before the recovery of sufficient brain-stem function to allow a stable vegetative state; the end stages of degenerative neurologic conditions, such as Alzheimer's or Creutzfeldt-Jakob disease; coma from untreatable mass lesions such as neoplasms or vascular masses; and anencephaly in infants.

Because of the diagnostic, prognostic, and therapeutic uncertainties concerning the persistent vegetative state, several professional medical organizations began a comprehensive examination of their standards of medical care for patients with this condition. In 1989, the American Academy of Neurology published a position paper that defined persistent vegetative state, classified artificial nutrition and hydration as forms of medical treatment, and stated that patients or their surrogates could decide to terminate treatment and that there were no medical or ethical distinctions between withholding and withdrawing treatment. A 1990 survey by the American Neurological Association found that 88 percent of responding members agreed with this document. In a 1991 survey by the Child Neurology Society, 92 percent of respondents agreed with the position paper as it related to adults, but only 72 percent thought that it was applicable to infants and children. In addition, 75 percent of the respondents to this survey indicated that they would not withdraw nutrition and hydration from children in a persistent vegetative state.

In 1990, the Council on Scientific Affairs and the Council on Ethical and Judicial Affairs of the American Medical Association issued a report that provided...
clinical criteria for the diagnosis of a persistent vegetative state and discussed ethical and legal implications of decisions to withhold or withdraw life-prolonging medical treatment — matters that were receiving widespread attention at the time.11-15 In 1991, the United Kingdom’s Institute of Medical Ethics Working Party on the Ethics of Prolonging Life and Assisting Death published a position statement indicating that a diagnosis of persistent vegetative state could usually be made with confidence three months after the acute insult but that in young children, the extent of damage and period of recovery were less predictable.16 More recently, the British Medical Association’s Medical Ethics Committee and the American Neurological Association have published position papers that define criteria for the clinical diagnosis of a persistent vegetative state and address several of the ethical issues concerning the care of patients in such a state.17,18

Because of the acceptance of recent consensus statements concerning guidelines for determining brain death in children19 and the medical aspects of anencephaly in infants,20 the Multi-Society Task Force on PVS was established in 1991 and charged with the creation of this document. Two representatives were appointed from each of the five societies, and an advisory panel of consultants was selected from the related fields of medicine, ethics, and law. The document was approved by the executive committee of each society.

Data reviewed by members of the task force were obtained from several sources, including a comprehensive literature review of all Medline references to the terms “vegetative state” and “persistent vegetative state,” a “request for information” published in medical journals supported by the five sponsoring societies, a review of stories in the popular media concerning unexpected recovery from prolonged coma, and data from the National Institute of Neurological Disorders and Stroke Traumatic Coma Data Bank.

This statement by the task force summarizes the medical facts about the persistent vegetative state; it does not address associated ethical, legal, or other issues. The statement is divided into two parts. The first defines persistent vegetative state and related terms and conditions and discusses the epidemiology, causes, and pathological features, as well as ancillary diagnostic studies. The second part addresses the prognosis for recovery and long-term survival of patients in a persistent vegetative state and discusses issues related to pain and suffering and treatment.

**Definition and Clinical Aspects**

The vegetative state is a clinical condition of complete unawareness of the self and the environment, accompanied by sleep–wake cycles with either complete or partial preservation of hypothalamic and brain-stem autonomic functions. The condition may be transient, marking a stage in the recovery from severe acute or chronic brain damage, or permanent, as a consequence of the failure to recover from such injuries. The vegetative state can also occur as a result of the relentless progression of degenerative or metabolic neurologic diseases or from developmental malformations of the nervous system.

The vegetative state can be diagnosed according to the following criteria: (1) no evidence of awareness of self or environment and an inability to interact with others; (2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness manifested by the presence of sleep–wake cycles; (5) sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing care; (6) bowel and bladder incontinence; and (7) variably preserved cranial-nerve reflexes (pupillary, oculocephalic, corneal, vestibulo-ocular, and gag) and spinal reflexes.

The distinguishing feature of the vegetative state is an irregular but cyclic state of circadian sleeping and waking unaccompanied by any behaviorally detectable expression of self-awareness, specific recognition of external stimuli, or consistent evidence of attention or intention or learned responses. Patients in a vegetative state are usually not immobile. They may move the trunk or limbs in meaningless ways. They may occasionally smile, and a few may even shed tears; some utter grunts or, on rare occasions, moan or scream. Some patients have acquired, nonhabitual startle myoclonus. Such activities are inconsistent, nonpurposeful, and coordinated only when they are expressed as part of a subcortical, instinctively patterned, reflexive response to external stimulation. These motor activities may misleadingly suggest purposeful movements, yet these responses have been observed in patients in whom careful study has disclosed no evidence of psychological awareness or the capacity to engage in learned behavior.

As a result of the relative preservation of brain-stem functions, most patients in a vegetative state retain good normal reflexive regulation of vision and eye movement. Some patients have unequal or irregular pupils or limited responses to vestibulo-ocular stimulation. A few patients may have signs of mild internuclear ophthalmoplegia or other oculomotor abnormalities related to the brain stem. Occasionally, one or both third nerves are paralyzed.

Sustained visual pursuit is lacking in most patients in a vegetative state. They do not fixate on a visual target, track moving objects with their eyes, or withdraw from threatening gestures. When patients undergo a transition from the vegetative state to a state of awareness, one of the first and most readily observable signs of this transition is the appearance of sustained visual pursuit. However, patients in a vegetative state often have inconsistent primitive auditory or visual orienting reflexes, characterized by a turning of the head and eyes toward peripheral
sounds or movements. In rare cases, patients who have no other evidence of consciousness over a period of months to years have some degree of briefly sustained visual pursuit or fixation, which is believed to be mediated through brain-stem structures. Nevertheless, one should be extremely cautious in making a diagnosis of the vegetative state when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures.

The capacity for survival in a persistent vegetative state requires preservation of hypothalamic and brain-stem autonomic functions. Most patients who survive for a long time maintain normal body temperature, the ability to breathe spontaneously, and a functioning cardiovascular system. The prognosis is worse if there are hypothalamic disturbances producing central fever, excess sweating, disturbances in salt and water metabolism, and refractory pulmonary problems. In most patients, the gag, cough, sucking, and swallowing reflexes are preserved. Except for a lack of coordination in chewing and swallowing, gastrointestinal function remains nearly normal. As the prolonged survival of some patients in a persistent vegetative state suggests, autonomic function is sufficient to maintain long-term internal regulation so long as external needs receive constant attention.

**RELATED TERMS AND CONDITIONS**

*Unconsciousness, Coma, and the Vegetative State*

The term “consciousness” was defined by William James in 1890 as awareness of the self and the environment. Consciousness has two dimensions: wakefulness and awareness. Normal consciousness requires arousal, an independent, autonomic-vegetative brain function subserved by ascending stimuli from the pontine tegmentum, posterior hypothalamus, and thalamus that activate wakefulness. Awareness is subserved by cerebral cortical neurons and their reciprocal projections to and from the major subcortical nuclei. Awareness requires wakefulness, but wakefulness can be present without awareness.

Unconsciousness implies global or total unawareness and is characteristic of both coma and the vegetative state. Patients in a coma are unconscious because they lack both wakefulness and awareness. Patients in a vegetative state are unconscious because, although they are wakeful, they lack awareness. In this report we use the terms awareness and consciousness interchangeably.

**Persistent as Compared with Permanent Vegetative States**

As originally defined by Jennett and Plum in 1972, the term “persistent,” when applied to the vegetative state, meant sustained over time; “permanent” meant irreversible. Notwithstanding Jennett and Plum’s precise use of language, confusion has arisen over the exact meaning of the term “persistent.” The adjective “persistent” refers only to a condition of past and continuing disability with an uncertain future, whereas “permanent” implies irreversibility. Persistent vegetative state is a diagnosis; permanent vegetative state is a prognosis.

A wakeful unconscious state that lasts longer than a few weeks is referred to as a persistent vegetative state. We define such a state operationally as a vegetative state present one month after an acute traumatic or nontraumatic brain injury or a vegetative state of at least one month’s duration in patients with degenerative or metabolic disorders or developmental malformations. A permanent vegetative state, on the other hand, means an irreversible state, which like all clinical diagnoses in medicine, is based on probabilities, not absolutes. A patient in a persistent vegetative state becomes permanently vegetative when the diagnosis of irreversibility can be established with a high degree of clinical certainty—that is, when the chance that the patient will regain consciousness is exceedingly small. We believe there are sufficient data on the prognosis for neurologic recovery to allow us to distinguish between persistent and permanent vegetative states. These data, in conjunction with other relevant factors in an individual patient, can be used by a physician to determine when the persistent vegetative state becomes permanent—that is, when a physician can tell the patient’s family or surrogate with a high degree of medical certainty that there is no further hope for recovery of consciousness or that, if consciousness were recovered, the patient would be left severely disabled.

**Diagnostic Factors and the Limits of Certainty**

By definition, patients in a persistent vegetative state are unaware of themselves or their environment. They are noncognitive, nonsentient, and incapable of conscious experience. There is, however, a biologic limitation to the certainty of this definition, since we can only infer the presence or absence of conscious experience in another person. A false positive diagnosis of a persistent vegetative state could occur if it was concluded that a person lacked awareness when, in fact, he or she was aware. Such an error might occur if a patient in a locked-in state (i.e., conscious yet unable to communicate because of severe paralysis) was wrongly judged to be unaware. Thus, it is theoretically possible that a patient who appears to be in a persistent vegetative state retains awareness but shows no evidence of it. In the practice of neurology, this possibility is sufficiently rare that it does not interfere with a clinical diagnosis carefully established by experts.

Several individual signs of unconsciousness, as well as a small number of laboratory tests, are very closely correlated with the diagnosis of the condition of unconsciousness that characterizes a persistent vegetative state. At present, these lines of evidence based on careful clinical and laboratory studies support the conclusion that patients in a persistent vegetative state are unaware of themselves or their environment. First, motor or eye movements and facial expressions
in response to various stimuli occur in stereotyped patterns that indicate reflexive responses integrated at deep subcortical levels rather than learned voluntary acts. The presence of these responses is consistent with complete unawareness. Second, positron-emission tomographic studies of regional cerebral glucose metabolism show levels far lower than those in patients who are aware or in a locked-in state. These low metabolic rates are comparable to those reported during deep general anesthesia in normal subjects whom all would agree are unaware and insensate.\textsuperscript{25,26} Finally, all available neuropathological examinations of the brains of patients with a clinical diagnosis of a persistent vegetative state show lesions so severe and diffuse that awareness would have been highly improbable, given our biologic understanding of how the anatomy and physiology of the brain contribute to consciousness.\textsuperscript{23,24}

An accurate diagnosis is critical. Errors in diagnosis have occurred because of confusion about the terminology used to describe patients in this condition, the inexperience of the examiner, or an insufficient period of observation.\textsuperscript{25} Physicians caring for such patients should be aware of these potential problems and be as precise and careful as possible when applying the suggested clinical criteria.\textsuperscript{26}

Related Conditions

Other conditions of severe neurologic disability or altered consciousness include coma, brain death, the locked-in syndrome, and dementia (Table 1).

Coma is deep, sustained pathologic unconsciousness that results from dysfunction of the ascending reticular activating system in either the brain stem or both cerebral hemispheres. The eyes remain closed, and the patient cannot be aroused. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least an hour.

Brain death is the permanent absence of all brain functions, including those of the brain stem. Brain-dead patients are irreversibly comatose and apneic and have lost all brain-stem reflexes and cranial-nerve functions. The standard clinical criteria for the diagnosis of brain death in adults, children, and newborn infants are outlined elsewhere.\textsuperscript{14,19,27-30}

The locked-in syndrome refers to a state in which consciousness and cognition are retained but movement and communication are impossible because of severe paralysis of the voluntary motor system.\textsuperscript{26,31} This condition may result from abnormalities in the descending corticospinal and corticobulbar pathways at or below the pons. In such cases, breathing is possible. The locked-in syndrome can also be associated with diseases of the peripheral motor nerves or paralysis produced by the administration of neuromuscular blocking agents. Patients with this syndrome can usually establish limited communication through eye-movement signals. Diagnosis of the locked-in syndrome is established by clinical examination. Brain imaging may show isolated ventral pontine infarction, and nerve-conduction studies may demonstrate severe peripheral neuropathy. Positron-emission tomographic scans have shown higher metabolic levels in the brains of patients in the locked-in state than in patients in a persistent vegetative state. Electroencephalograms, evoked responses, and single-photon-emission computed tomograms do not distinguish reliably between the locked-in and vegetative states.

Dementia is a condition of progressive, multidimen-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Self-Awareness</th>
<th>Sleep-Wake Cycles</th>
<th>Motor Function</th>
<th>Experience of Suffering</th>
<th>Respiration Function</th>
<th>EEG Activity</th>
<th>Cerebral Metabolism*</th>
<th>Prognosis for Neurologic Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent vegetative state</td>
<td>Absent</td>
<td>Intact</td>
<td>No purposeful movement</td>
<td>No</td>
<td>Normal</td>
<td>Polymorphic delta or theta, sometimes slow alpha</td>
<td>Reduced by 50% or more</td>
<td>Depends on cause (acute traumatic or nontraumatic injury, degenerative or metabolic condition, or developmental malformation)</td>
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<tr>
<td>Coma</td>
<td>Absent</td>
<td>Absent</td>
<td>No purposeful movement</td>
<td>No</td>
<td>Depressed, variable</td>
<td>Polymorphic delta or theta</td>
<td>Reduced by 50% or more (depends on cause)</td>
<td>Usually recovery, persistent vegetative state, or death in 2 to 4 weeks</td>
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<tr>
<td>Brain death</td>
<td>Absent</td>
<td>Absent</td>
<td>None or only reflex spinal movements</td>
<td>No</td>
<td>Absent</td>
<td>Electroencephalogram silence</td>
<td>Absent</td>
<td>No recovery</td>
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<tr>
<td>Locked-in syndrome</td>
<td>Present</td>
<td>Intact</td>
<td>Quadriparesis and pseudobulbar palsy; eye movement preserved</td>
<td>Yes</td>
<td>Normal</td>
<td>Normal or minimally abnormal</td>
<td>Minimally or moderately reduced</td>
<td>Recovery unlikely; persistent quadriparesis with prolonged survival possible</td>
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<td>Akinetic mutism</td>
<td>Present</td>
<td>Intact</td>
<td>Paucity of movement</td>
<td>Yes</td>
<td>Normal</td>
<td>Non-specific slowing</td>
<td>Unknown</td>
<td>Recovery very unlikely (depends on cause)</td>
</tr>
<tr>
<td>Dementia</td>
<td>Present but lost in late stages</td>
<td>Intact</td>
<td>Variable; limited with progression</td>
<td>Yes but lost in late stages</td>
<td>Normal</td>
<td>Non-specific slowing</td>
<td>Variously reduced</td>
<td>Irreversible (ultimately outcome depends on cause)</td>
</tr>
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</table>

*This table provides a general overview of the persistent vegetative state and related neurologic conditions. Because of the overlap between clinical and laboratory findings, these characteristics will not apply to every patient. Neuroimaging studies (magnetic resonance imaging or computed tomography) may be useful in the clinical evaluation of patients but may not always be helpful in differentiating among these conditions. EEG denotes electroencephalographic.

\textsuperscript{1}Determined by positron-emission or single-photon-emission computed tomography.
sional loss of cognitive functions in which arousal mechanisms are usually normal. Advanced dementia can progress until patients lose their self-awareness and all evidence of learned behavior. At this point, such patients are in a vegetative state.

Three other conditions deserve mention. Akinetic mutism is a rare syndrome characterized by pathologically slowed or nearly absent bodily movement and loss of speech. Wakefulness and self-awareness may be preserved, but the level of mental function is reduced. The condition characteristically accompanies gradually developing or subacute bilateral damage to the paramedian mesencephalon, basal diencephalon, or inferior frontal lobes. Necortical death is a term used by some authors to refer to a persistent vegetative state, but in addition to the characteristics of a persistent vegetative state, necortical death is marked by an absence of or substantial slowing of electrocortical activity on electroencephalography. Others equate necortical death with the ostensible death of all neurons of the cerebral cortex. It is not clear, therefore, whether this term denotes a clinical syndrome or its electrical, pathologic, or anatomical features. Apallic syndrome is an archaic term for a condition that is now considered equivalent to a persistent vegetative state. The terms “necortical death” and “apallic state” have limited usefulness and should be abandoned, because they do not represent distinct clinical entities.

Epidemiology

The prevalence of persistent vegetative state is not known because of the lack of accepted diagnostic criteria and the fact that, until recently, neither the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), nor most health agencies included persistent vegetative state as a codable diagnosis. According to estimates, however, in the United States there are 10,000 to 25,000 adults and 4,000 to 10,000 children in a persistent vegetative state.6,10,11,15,16,33-47

Causes and Clinical Course

The clinical course of a persistent vegetative state depends on the particular underlying disease process.

Acute Traumatic and Nontraumatic Injuries

The most common acute causes of the vegetative state in adults and children are head trauma and hypoxic–ischemic encephalopathy (Table 2). The clinical course after the acute insult usually begins with coma (with eyes closed) for several days to weeks, during which time the acute illness stabilizes and the stunned but ultimately viable brain stem and lower diencephalon resume function. By this time, most patients are able to breathe spontaneously and no longer require ventilatory assistance. After the interval of coma, spontaneous opening of the eyes, random eye movements, blinking, and limb movements occur, along with sleep–wake cycles. In a few patients, the vegetative state occurs immediately after the insult, without an initial period of coma.

Table 2. Causes of the Persistent Vegetative State in Adults and Children.*

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<tr>
<th>Causes of the Persistent Vegetative State in Adults and Children.</th>
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<tr>
<td>Acute Injuries</td>
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<td>Traumatic</td>
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<td>Motor vehicle accidents</td>
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<td>Gunshot wound or other form of direct cerebral injury</td>
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<td>Nonaccidental injury in children</td>
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<td>Birth injury</td>
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<td>Nontraumatic</td>
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<td>Hypoxic ischemic encephalopathy</td>
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<td>Cardiorespiratory arrest</td>
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<td>Perinatal asphyxia</td>
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<td>Pulmonary disease</td>
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<td>Prolonged hypotensive episode</td>
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<td>Near-drowning</td>
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<td>Suffocation or strangulation</td>
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<td>Cerebrovascular injury</td>
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<td>Cerebral hemorrhage</td>
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<td>Cerebral infarction</td>
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<td>Subarachnoid hemorrhage</td>
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<td>CNS infection</td>
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<td>Bacterial meningitis</td>
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<td>Viral meningoencephalitis</td>
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<td>Brain abscess</td>
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<td>CNS tumor</td>
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<td>CNS toxins or poisoning</td>
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<td>Degenerative and metabolic disorders</td>
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<td>In adults</td>
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<tr>
<td>Alzheimer’s disease</td>
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<td>Multi-infarct dementia</td>
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<td>Pick’s disease</td>
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<td>Creutzfeldt–Jakob disease</td>
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<td>Parkinson’s disease</td>
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<td>Huntington’s disease</td>
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<td>In children</td>
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<td>Ganglioside storage disease</td>
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<td>Adrenoleukodystrophy</td>
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<td>Neuronal ceroid lipofuscinosis</td>
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<td>Organic aciduria</td>
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<td>Mitochondrial encephalopathy</td>
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<td>Gray-matter degenerative disorders</td>
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<td>Developmental malformations</td>
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<td>Anencephaly</td>
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<td>Hydranencephaly</td>
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<td>Lissencephaly</td>
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<td>Holoprosencephaly</td>
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<td>Encephalocele</td>
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<td>Schizencephaly</td>
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<td>Congenital hydrocephalus</td>
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<tr>
<td>Severe microcephaly</td>
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</table>

*Includes only the most common disorders that have been reported to cause a persistent vegetative state in each of the three categories. CNS denotes central nervous system.
pairment of eye opening, the presence of abnormal oculocephalic or motor responses, and the inability to obey commands at two weeks are all correlated with a vegetative outcome.56

**Degenerative and Metabolic Disorders**

Many degenerative and metabolic nervous system disorders in adults and children inevitably progress to an irreversible vegetative state. The early stages of such disorders are marked by progressive impairment of intellect, memory, language, motor skills, and social behavior, yet many patients retain some degree of awareness of themselves and their environment. In later stages, awareness disappears, marking the start of a vegetative state.

In patients with degenerative diseases, a persistent vegetative state usually evolves over a period of several months or years.57 Those who remain in a vegetative state may die of a superimposed infectious illness. Those who survive such an illness remain in a vegetative state or go into a coma. Patients with degenerative diseases who have severe impairment but retain some degree of awareness may lapse briefly into a vegetative state from the effects of medication, infection, superimposed medical or surgical illnesses, seizure activity, or decreased fluid and nutritional intake.57 The possibility of such a temporary metabolic or toxic encephalopathy must be eliminated before establishing that the patient is in a persistent vegetative state.58

**Developmental Malformations**

Severe congenital malformations of the nervous system in infants and children may prevent the development of awareness or cognition. Among the malformations associated with the developmental vegetative state are anencephaly and hydranencephaly (Table 2). Diagnosis of the vegetative state in infants and children poses several problems related to the immaturity of the developing brain and the ongoing influences of development on the potential for reorganization of structure and function.59

On the basis of our understanding of development, the diagnosis of the vegetative state may be difficult to make in infants younger than three months, except in the case of infants with anencephaly. Newborns and young infants have a limited ability to show higher cognitive functions before this age.58,69 Although they are capable of a variety of social responses, including visual and auditory orientation, cuddling, the ability to be consoled, and self-quieting behavior, these responses may be tenuous, inconsistent, and unsustained until three months of age.61,62 The concept of the vegetative state cannot be applied to preterm infants because of developmental immaturity and, to a lesser extent, the lack of consistently recognizable sleep-wake cycles.63,64

Recognition of the vegetative state in infants and young children also depends on the ability to distinguish between voluntary and involuntary respons-

e. Differentiation of voluntary from involuntary responses may be unreliable until approximately three months of age. Voluntary behavior that can be elicited includes a consistent and sustained response of turning to or following visual or auditory stimuli, a growing awareness of social stimuli, cuddling in response to interactions experienced as comforting, and a preference for a specific behavior when several choices are presented. Involuntary behavior includes blinking or wandering, nonpurposeful eye movements; nonspecific sounds and grimace-like expressions in reaction to noxious stimuli; and primitive reflexes, including grasp, postural, startle, and alerting responses.

Some newborn infants with severe developmental malformations, such as hydranencephaly, have a minimal cerebral cortex or none. Such infants usually remain in a developmental vegetative state. Because some brain tissue is developing, these infants may have a limited awareness of their environment and minimal purposeful motor activity within the first several months of life.67,68 However, only limited improvement has been reported in such children. Those with less extensive malformations (such as certain types of holoprosencephaly or lissencephaly) may appear to be in a vegetative state as infants but eventually show some evidence of awareness and responsiveness. Such infants generally continue to have severe disabilities. There are few reports describing the clinical course of such patients, but some degree of consciousness may emerge.

**Pathologic Features**

The anatomical basis for a persistent vegetative state differs somewhat from case to case, for several reasons. The interval between brain injury and death affects the nature and severity of pathologic changes. Patients in a vegetative state who die early of medical complications are unlikely to undergo neuropathologic changes that would be sufficient to cause chronic unconsciousness in long-term survivors. Furthermore, in patients with chronic neurologic conditions, other complicating factors, such as severe atherosclerotic disease, may independently injure the brain. In such patients, it may be difficult to determine at autopsy exactly which neuropathologic changes accompanied the initial failure to recover consciousness.

Allowing for the above limitations, two major patterns have characterized most detailed reports on the neuropathology of a persistent vegetative state due to acute traumatic or nontraumatic brain injury. We are not aware of any systematic investigation of the neuropathologic characteristics of patients in whom a persistent vegetative state was due to degenerative, metabolic, or developmental disorders.

**Diffuse Laminar Cortical Necrosis**

This pattern follows acute, global hypoxia and ischemia. The principal finding is extensive multifocal or diffuse laminar cortical necrosis with almost invari-
able involvement of the hippocampus. These abnormalities may be accompanied by scattered small areas of infarction or neuronal loss in the deep forebrain nuclei, hypothalamus, or brain stem.\textsuperscript{25,68} Relatively selective thalamic necrosis may also follow acute global ischemia, although the specific anatomical boundaries for this uncommon pattern have not been well described\textsuperscript{50} (and see the report, elsewhere in this issue of the Journal, on studies of the brain of Karen Ann Quinlan).\textsuperscript{71}

**Diffuse Axonal Injury**

This abnormality is usually due to a shearing injury after acute trauma. An extensive subcortical axonal injury virtually isolates the cortex from other parts of the brain.\textsuperscript{41} Sometimes a diffuse axonal injury is accompanied by small primary brain-stem injuries, as well as secondary damage to the brain stem that results from transtentorial herniation soon after the injury.\textsuperscript{72,74} In patients with an axonal injury complicated by acute circulatory or respiratory failure, diffuse laminar necrosis may also be present.

Only a few pathological reports on the persistent vegetative state describe severe abnormalities of the brain stem. Those that do mainly concern patients in whom severe paramedian mesencephalic damage developed secondary to acute downward or upward transtentorial herniation during the early stage of illness. Lesions confined to the brain stem seldom, if ever, cause long-term unconsciousness, although there has been a report of four patients with severe secondary brain-stem damage in whom coma persisted for as long as six weeks before death.\textsuperscript{75} We have found no well-described autopsy studies of patients in a persistent vegetative state who had severe damage confined to the hypothalamus.

**Ancillary Diagnostic Studies**

Neurodiagnostic tests alone can neither confirm the diagnosis of a vegetative state nor predict the potential for recovery of awareness.\textsuperscript{88} However, when used in conjunction with a clinical evaluation, laboratory tests may provide useful supportive information.

**Electroencephalography**

In most patients in a persistent vegetative state, electroencephalograms (EEGs) show diffuse generalized polymorphic delta or theta activity.\textsuperscript{76,77} This pattern is usually not attenuated by sensory stimulation, except occasionally by noxious stimulation.\textsuperscript{78,79} In most patients, the transition from wakefulness to sleep is accompanied by some desynchronization of the background activity.\textsuperscript{90} In some patients, very-low-voltage EEG activity is all that can be detected. In others, persistent alpha activity is the most remarkable feature. In approximately 10 percent of patients in a vegetative state, the EEG is nearly normal late in the course of illness but without evidence of vision-induced alpha blocking.\textsuperscript{77} There have been occasional reports of isoelectric EEGs in patients in a vegetative state.\textsuperscript{37,58,76,81,82} Most investigators have not reported this finding, however, nor has it been confirmed by reviews of the initial EEG records by other investigators. Typical epileptiform activity is unusual in patients in a persistent vegetative state, as is seizure activity.

The transition from coma to the vegetative state is not accompanied by notable changes in the EEG. However, clinical recovery from the vegetative state may be paralleled by diminished delta and theta activity and the reappearance of a reactive alpha rhythm.\textsuperscript{76,78} This phenomenon is inconsistent and does not predict future recovery.\textsuperscript{77,78}

Compressed spectral analysis of the EEG has been used to study patients with prolonged unconsciousness. Preliminary data suggest that patients with changeable or desynchronized spectrograms and abnormal evoked responses remain in a vegetative state.\textsuperscript{83}

Infants and children have abnormalities on the EEG that are similar to those reported in adults, although in infants and children the EEG activity may be somewhat more discontinuous and of lower voltage.\textsuperscript{66,64}

**Evoked-Response Studies**

Evoked-response testing is useful statistically, but not always clinically, in trying to assess the risk of a vegetative outcome in patients who are in a coma as a result of an acute neurologic injury.\textsuperscript{85} Somatosensory evoked responses are the most sensitive and reliable markers in both adults and children.\textsuperscript{86-91} The bilateral absence of such responses one week after the insult is highly predictive of failure to regain consciousness (i.e., of death or survival in a vegetative state). Patients without somatosensory evoked responses, however, may recover at least minimal cognitive activity, especially if the coma is traumatic rather than anoxic.\textsuperscript{92,93} In contrast, patients with normal somatosensory responses may enter a vegetative state and remain in it.\textsuperscript{88} Prolongation of the central conduction time of an evoked response is a less reliable finding than the absence of a response in predicting a poor outcome.\textsuperscript{78,84,95}

Other evoked potentials, such as the brain-stem auditory evoked response, are of limited value. Numerous studies have shown that the brain-stem auditory evoked response is preserved when the somatosensory evoked response is absent, and the outcome is either survival in a vegetative state or death.\textsuperscript{78,90,97} Multimodal evoked-response testing may be used to determine the outcome, but whether the results are of greater predictive value than the somatosensory evoked response alone remains uncertain. The presence of P\textsubscript{200} evoked responses is not necessarily correlated with the outcome.\textsuperscript{96}

**Neuroimaging**

Computed tomographic or magnetic resonance imaging in patients in a persistent vegetative state often
reveals diffuse or multifocal cerebral disease involving the gray and white matter. Although there are no established correlations between the results of neuroimaging studies and the development of the vegetative state or the potential for recovery, most patients who do not recover consciousness have abnormal scans. When studied during the first several months after a traumatic or nontraumatic brain injury, patients in a persistent vegetative state are more likely to recover consciousness yet remain severely disabled if serial neuroimaging scans are normal than if they are abnormal. Serial scanning usually documents progressive brain atrophy, which reduces the likelihood of neurologic recovery.

### Cerebral Metabolic Studies

A substantial reduction in the cerebral metabolic rate has been reported in approximately 20 adults in a persistent vegetative state. A 40 to 60 percent reduction in global cerebral oxidative metabolism was observed in six patients in a vegetative state after trauma or diffuse anoxia. Positron-emission tomographic (PET) studies showed a 50 to 60 percent decrease in the glucose metabolic rate in the cerebral cortex, basal ganglia, and cerebellum in seven adults; no overlap in metabolic impairment was noted when these patients were compared with three patients who had the locked-in syndrome. Using the same method, other investigators found a 50 percent reduction in cerebral glucose metabolism in patients in a vegetative state, as compared with a 25 percent reduction in metabolic activity in patients who had regained consciousness after anoxic cerebral injuries. The parieto-occipital and mesiorfrontal regions had the most consistent reduction in metabolic activity, whereas Levy et al. reported consistently low metabolic rates in all cortical areas.

Although these studies demonstrate substantial reductions in the metabolism of glucose, there is not yet sufficient information to warrant the use of PET scanning to determine prognosis. Likewise, the lack of experience with cerebral metabolic studies in infants and children in a vegetative state precludes the use of such studies to assess prognosis in infants and children. Normal cerebral metabolic activity in this age group is substantially lower than that reported in adults. Questions have been raised about the validity of cerebral metabolic studies to determine whether patients in a vegetative state are conscious or can experience pain and suffering. These questions remain unanswered and require further systematic investigation. Whether patients are conscious and have the potential to experience pain and suffering can best be assessed by careful and repeated neurologic examinations.

### Cerebral Blood Flow

Measurement of cerebral blood flow immediately after an acute neurologic injury does not predict a vegetative outcome in either adults or children. Once a vegetative state exists, however, cerebral blood flow is likely to be reduced. An early study using xenon-133 in four patients in a vegetative state found that cerebral blood flow was 10 to 20 percent of normal. PET studies in seven patients in a persistent vegetative state who were studied 3 weeks to 68 months after acute injury showed a 50 percent decrease in cerebral blood flow. More recent radiouclide-imaging studies using HM-PAO—single-photon-emission computed tomography showed a global reduction in cerebral blood flow 2 to 12 months after a head injury, as well as 3 years later. Some studies, however, have found normal cerebral blood flow in patients in a persistent vegetative state.

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