# V TRAUMATIC BRAIN INJURY

Andres M. Salazar, m.d.

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults in the United States; the total national cost of TBI is more than $39 billion a year.[1] Elucidation of the pathophysiology of brain injury is an important challenge for physicians who care for TBI patients. Equally important are prevention and a better scientific understanding of recovery and rehabilitation.

TBI is now generally viewed as a multidimensional, dynamic process. It is not unusual for a patient with TBI who initially is relatively stable and awake or in a light coma to deteriorate rapidly. Delayed hematoma or expanding contusions that are amenable to surgery account for many such cases. Others are related to uncontrolled brain swelling that may not respond to conventional management. Delayed secondary injury at the cellular level is also a major contributor to brain swelling and tissue loss after TBI. The ultimate pathologic picture thus evolves during the first few hours and days after trauma, and the physiologic, clinical, and behavioral aspects of recovery can continue for years. For these reasons, therapy should be predicated on an understanding of the multidimensional pathology of TBI and its evolution.

TBI is traditionally classified by its severity [*see Table 1*], though the current definitions are imperfect and distinctions between mild, moderate, and severe head injury can be difficult to make in the acute period. For example, acute management of an unconscious patient with a moderate head injury may differ little from that of a comatose patient with a more severe head injury; or a patient with little or no initial loss of consciousness may harbor a more serious and even life-threatening pathology, such as a delayed hematoma. Nevertheless, the distinctions are generally useful in guiding the approach to the patient.

## Etiology

Brain injury may be caused by any of several types of head trauma, including the more typical closed head injury (in which rapid acceleration or deceleration causes the brain to strike the inside of the skull), direct impact to the head, or penetration by a missile or other foreign object. Although some details of the pathology of these types of trauma may differ, acute and long-term management are similar in most cases.

## Pathogenesis

The pathologic changes that occur in TBI may result less from the injury itself than from an uncontrolled vicious circle of biochemical and physiologic events set in motion by the trauma. These biochemical events include changes in arachidonic acid metabolites (e.g., the prostaglandins); the formation of oxygen free radicals and lipid peroxidation; and changes in electrolytes (e.g., calcium and magnesium) in excitotoxic neurotransmitters (e.g., glutamate) and changes in various kinins and cytokines.[2] These events can result in progressive injury to otherwise viable brain tissue by altering vascular reactivity and producing further ischemia, by producing brain swelling (hyperemia, edema, or both), by injuring neurons and glia directly, or by activating macrophages that cause neuronal and glial injury. The patient with severe TBI also often has multiple systemic abnormalities—such as changes in nutrition, cardiopulmonary status,[3] circulating catecholamines, and coagulation[4]—that may be directly related to the brain injury and may have a profound impact on treatment.

At least five parallel components of the pathology of closed head injury have been identified: (1) focal hematomas and contusions, (2) diffuse axonal injury, (3) diffuse microvascular injury with loss of autoregulation and acute brain swelling, (4) hypoxia-ischemia, and (5) selective neuronal loss (especially of thalamic reticular, hippocampal, and cerebellar neurons), possibly caused by excitotoxins. In addition, recent electrophysiologic evidence suggests that a diffuse neuronal (gray matter) dysfunction may be the most subtle and sensitive measure of mild TBI and concussion [*see* Diffuse Gray Matter Dysfunction, *below*]. Each component may have a different effect on the patient, depending on the patient's premorbid status, the severity of the injury, the treatment given, and the time that has elapsed since injury.

Some of these pathologic processes, such as focal hematomas and microvascular injury with brain swelling, can result in the death of the patient soon after injury; others, such as diffuse axonal injury and excitotoxic injury, may result principally in the death of neuronal groups and thus have implications for long-term function. Evaluation of the clinical efficacy of specific therapies therefore depends on the particular pathology targeted by the treatment. For example, survival after TBI may be a good outcome measure of the efficacy of agents designed to limit subacute brain swelling, but it may not be a good measure for evaluating potentially neuron-sparing agents, such as certain glutamate antagonists and neurotrophins.

### Focal Injury

Focal injuries include intracerebral and extracerebral hematomas and focal contusions. Hematomas are most common after the rapid acceleration or deceleration that occurs as

*Table 1* Severity of Traumatic Brain Injury

| *Severity* | *Admission GCS Score* | *Duration of Unconsciousness* | *Duration of Posttraumatic Amnesia* | *CT/MRI* |
|---|---|---|---|---|
| Uncomplicated mild | 13–15 | 0–20 min | < 24 hr | Normal |
| Complicated mild | 13–15 | 0–20 min | < 24 hr | Abnormal |
| Moderate | 9–12 | < 24 hr | > 24 hr | Usually abnormal |
| Severe | 3–8 | > 24 hr | Weeks | Abnormal |

GCS—Glasgow Coma Scale

the result of a fall or another form of impact, especially in the elderly. Delayed hematomas, which can occur in patients who are initially at low risk but whose condition deteriorates rapidly, are particularly important. Small hematomas can be treated conservatively, but delaying the surgical removal of large hematomas for longer than 4 hours after injury significantly increases mortality and morbidity.

Focal contusions may occur under the site of impact, but by far the most common locations after acceleration-deceleration injury are in the orbitofrontal and anterior temporal lobes, where the brain abuts the base of the skull. The most troubling clinical sequelae are usually behavioral and cognitive abnormalities referable to these areas of the brain. Contusions can undergo secondary expansion or result in delayed hematomas. Patients with such injuries require particularly close observation in the acute period. Both hematomas and contusions are also significant risk factors for the development of posttraumatic epilepsy [*see 11:XII Epilepsy*].

### DIFFUSE AXONAL INJURY

Diffuse axonal injury—a shearing injury of axons in the hemispheric white matter, corpus callosum, and brain stem[5]—is a significant cause of persistent, severe neurologic deficits in closed-head injury. When severe, the injury is manifested clinically by immediate and prolonged loss of consciousness. Petechial hemorrhages in the white matter or blurring of the gray matter–white matter junction is best seen on magnetic resonance imaging, especially in coronal slices. However, the only early abnormality may be microscopic focal cytoskeletal disruption. These changes lead to disturbance of axonal flow and the subsequent severing of axons, with the typical light microscopic picture appearing 12 to 24 hours later. If severe enough, such axonal injury can lead to wallerian degeneration and diffuse target deafferentation.[6,7] It is possible that medical treatments can prevent total axonal disruption. Certain neurotrophins, such as brain-derived neurotrophic factor and perhaps insulinlike growth factor, may attenuate it.[8]

Such axonal injury may also occur even after mild TBI (MTBI) and in the absence of morphopathologic change in any other vascular, neural, or glial element. Some of the cognitive changes seen after MTBI may relate to diffuse axonal injury.

### DIFFUSE MICROVASCULAR DAMAGE

Diffuse microvascular damage is a major component of both closed and penetrating TBI. Depending on the severity of the injury, early changes may include loss of cerebrovascular autoregulation, with decreased responses to changes in carbon dioxide and perfusion pressure, and transient systemic hypertension. The loss of autoregulation makes the brain particularly susceptible to fluctuations in systemic blood pressure; otherwise tolerable hypotension can thus result in cerebral ischemic damage in the patient with TBI. In addition, altered vascular sensitivity to circulating catecholamines can lead to vasoconstriction and further focal ischemia or reperfusion injury. The microvascular pathology includes an endothelial change that probably involves oxygen free radical–induced decreases in endothelial nitric oxide, with a concomitant vasoconstriction, and an initial hyperglycolysis with a dissociation of cerebral blood flow and metabolism.[9] Positron emission tomography has demonstrated these metabolic changes even in patients with MTBI.

Free radicals, including the superoxide radical peroxynitrite, and the process of lipid peroxidation play a critical role in secondary injury, not only by their effect on the microvasculature but also by their direct effects on tissue. The pharmacologic agents used to reduce the formation of free radicals or to scavenge those already formed include steroids to inhibit lipid peroxidation; α-tocopherol (vitamin E) and its analogues; α-lipoic acid; iron chelators, such as deferoxamine; and enzymes such as superoxide dismutase. However, in phase III clinical studies, two such compounds—the 21-aminosteroid tirilazad mesylate and a polyethylene glycol–conjugated superoxide dismutase—failed to provide clear benefit to patients with acute, severe TBI.[10,11]

### HYPOXIA-ISCHEMIA

The classic pathology of hypoxia-ischemia primarily involves the hippocampus and the vascular border zones of the brain. It is often superimposed on other, more specific pathologies of TBI. The traumatized brain is particularly sensitive to hypoxia-ischemia, possibly because of the metabolic demands already placed on neurons by the trauma itself[12] or by increasing vascular permeability.[13] The most significant improvements in the survival of patients with TBI have resulted from recognition of the importance of this component and its prevention, largely through training of paramedics, the development of emergency transport systems, and immediate resuscitation protocols.[14]

### SELECTIVE NEURONAL VULNERABILITY, EXCITOTOXIC INJURY, AND NEURONAL ENERGY FAILURE

Selective vulnerability of certain neuronal groups, including hippocampal and thalamic reticular neurons that receive glutaminergic afferents from the orbitofrontal cortex, occurs after head injury and appears to be caused by glutamate excitotoxicity.[15] It also occurs after mild head injury in animal models and may be a cause of the fatigue, attention, and memory problems often seen in postconcussion syndrome in humans.

Excitotoxic injury may be one of the most important mechanisms of neuronal death after traumatic or ischemic injury. Excessive release of glutamate and other neurotransmitters unleashes a chain of cellular events that deplete neuronal energy stores, damage mitochondria, and result in cell death or apoptosis. Thus, glutamate antagonists or other neuroprotectants, such as dextrorphan, riluzole, memantine, and magnesium, may play a role in the acute treatment of TBI. However, because of the importance of glutamate in the brain, receptor blockade is usually accompanied by intolerable side effects; a number of clinical trials with such agents have failed to show a clear benefit.[16] Alternatively, therapies that prevent depletion of neuronal metabolic stores or that enhance neuronal stores have also been shown to protect cells in models of glutamate toxicity. One related neuroprotective strategy that reduces glutamate release and appears to protect cellular energy metabolism is moderate systemic hypothermia. A controlled pilot study showed long-term benefit from treatment with hypothermia for patients surviving severe TBI.[17] However, a larger multicenter study failed to confirm these findings.[18]

A more direct approach may be to use agents that enhance neuronal energy metabolism and mitochondrial function after injury. Because it addresses a "final common path" in neuronal dysfunction, death, or both, this approach may protect against various stressors, including excitotoxic, oxidative, or calcium-induced injury.[19] Depletion of neuronal energy can result because of the increased demands placed on neurons and their membrane pumps by the injury and because of a failure of adenosine triphosphate (ATP) production.

Mitochondrial dysfunction has been demonstrated after brain injury. One mechanism of mitochondrial dysfunction is the fail-

ure of the mitochondrial membrane, with consequent release of cytochrome-c into the cytoplasm and the subsequent activation of caspases and the apoptotic cascade. Similarly, it has been postulated that mitochondrial failure, including failure of the pyruvate dehydrogenase pathways, may underlie the demonstrated uncoupling of blood flow and metabolism after TBI.[19]

Cyclosporine has been demonstrated to have a neuroprotective effect, which is achieved through stabilization of the mitochondrial membrane.[20,21] Both creatine and the three-carbon sugar pyruvate have been shown to have marked neuroprotective effects in animal models of TBI. As with cyclosporine, this effect is achieved through stabilization of the mitochondrial membrane.[22,23] Pyruvate is not only the primary energy substrate in neuronal mitochondria but also a good scavenger of oxygen free radicals. Both pyruvate and creatine are inexpensive and nontoxic; they are in early clinical trials for the treatment of brain injury.

#### DIFFUSE GRAY MATTER DYSFUNCTION

In addition to selective neuronal vulnerability, recent evidence from quantitative electroencephalograhic and quantitative MRI studies suggests that a very common effect of TBI may be a diffuse gray matter dysfunction that manifests itself primarily through changes in brain electrical activity, as measured by EEG coherence, phase, and power.[24-27] These alterations may, in turn, reflect a relative loss of neuronal membrane electrical efficiency, probably as a consequence of the failure of neuronal energy metabolism and the ATP-driven neuronal ion pumps. Such failure would not be unexpected in the face of a probable diffuse excitotoxic challenge or other challenges in the early period after TBI. These alterations may be the only physiologic or pathologic evidence of MTBI or concussion. Although the pathology of this dysfunction is likely to be very subtle, there is a strong correlation between these changes and changes in the $T_2$-weighted MRI signal in the gray matter, which in turn is thought to reflect the functional integrity of neuronal membranes ($T_2$ refers to spin-spin, or transverse, relaxation time). These EEG changes have also been demonstrated to correlate with neuropsychological performance, suggesting that they could also be responsible for some of the cognitive changes that occur after MTBI. Restoration of neuronal energy metabolism might be expected to ameliorate these cognitive changes.

### Mild Traumatic Brain Injury

With an incidence of 180 per 100,000 people, MTBI is more common than any other neurologic diagnosis except migraine. MTBI is variably defined as any TBI/concussion with loss of consciousness of 0 to 30 minutes, a Glasgow Coma Scale (GCS) score of 13 to 15 on admission [*see Table 2*], posttraumatic amnesia or confusion lasting less than 24 hours, and no evidence of contusion or hematoma on CT. Concussion can be further divided into grades I, II, and III. Grade I concussion is characterized by transient mental changes lasting longer than 15 minutes, with no loss of consciousness; in grade II concussion, transient mental changes last longer than 15 minutes, and there is no loss of consciousness; and grade III concussion is characterized by brief loss of consciousness. Although these distinctions, especially the distinction between grade I and grade II concussion, can be relatively subtle, they can serve as a useful guide for return to normal activity, especially in athletes or other active individuals.[28] In any case, MTBI, even without loss of consciousness, has been repeatedly associated with measurable abnormalities in cognition, attention, and behavior, as well as documented quantitative EEG and neuropathologic changes.[24,29] Abnormalities seen on assessments of cognitive task have been repeatedly documented after MTBI; these abnormalities usually include disturbances of attention, information processing, and memory.[30-33] As might be expected, MTBI also has a significant psychosocial impact.

Over 75% of MTBI patients report some somatic or cognitive symptoms over the first several weeks after injury; these can have important functional, social, and economic implications. Symptoms include headache, dizziness or vertigo, blurred vision, fatigue, sleep disturbance, irritability, depression, anxiety, and poor memory and concentration. Typically, these symptoms improve steadily and are largely cleared after the first 3 months after injury. However, some symptoms, especially the emotional symptoms, can persist longer. The term postconcussion syndrome is often applied when this complex of symptoms is persistent.[30]

There has been increasing attention paid to MTBI in sports.[34] The study of MTBI in athletes offers several advantages, including the generally high preinjury health and motivation of athletes, the ability to conduct preinjury testing, and the relative predictability of the time of the injury. In one study, college football players were examined before and after injury; significant attention deficits were found to persist for as long as 5 days after a minor "ding" that was not associated with loss of consciousness.[35] Similar findings have been reported in soccer players.[36]

#### PATHOGENESIS

The pathology associated with MTBI or concussion is still unclear, but some evidence suggests that these injuries may be associated with a diffuse cortical neuronal dysfunction; selective vulnerability of certain neurons and a modest amount of diffuse axonal injury may also be factors. Microvascular injury with alterations in autoregulation and uncoupling of blood flow and metabolism has also been described in MTBI, especially with repeated MTBI—the so-called second impact syndrome—in pediatric and adolescent patients.[9,37,38] Finally, hematomas occur with some frequency in patients who might otherwise be classified as having MTBI.[39-41]

*Table 2* Glasgow Coma Scale[92]

| *Test* | *Response* | *Score* |
|---|---|---|
| Eye opening | Spontaneous | 4 |
| | To speech | 3 |
| | To pain | 2 |
| | None | 1 |
| Best verbal response | Oriented | 5 |
| | Confused | 4 |
| | Inappropriate | 3 |
| | Incomprehensible | 2 |
| | None | 1 |
| Best motor response (arm) | Obedience to commands | 6 |
| | Localization of pain | 5 |
| | Withdrawal response to pain | 4 |
| | Flexion response to pain | 3 |
| | Extension response to pain | 2 |
| | None | 1 |

*a* *b*

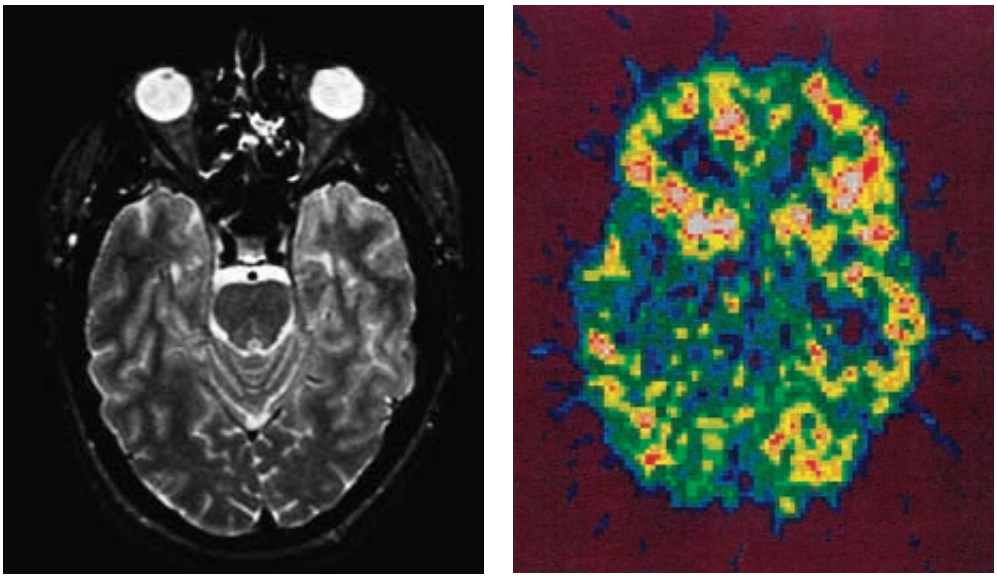

*Figure 1* **(*a*) MRI in a 25-year-old man with mild to moderate traumatic brain injury and residual irritability, lability of affect, aggressivity, and occasional dyscontrol episodes initially seems normal but on closer scrutiny shows blurring of the gray matter–white matter junction in the left temporal lobe. (*b*) Positron emission tomography confirms decreased metabolism in the left temporal lobe.**

### EVALUATION AND ACUTE MANAGEMENT

Although the emergency department evaluation and management of MTBI is controversial, the principal concern is with identifying evolving surgical lesions such as hematomas and contusions. The cause of injury can be a factor in management; for example, motor vehicle accidents involving large forces or impact to the head may raise the likelihood of hematomas, as do falls in older patients, especially if the patient is taking anticoagulants or aspirin. Documentation of the history of the injury, as well as the length of the period of unconsciousness, mental confusion, or both, can be very helpful in both acute and long-term management. In the past, many patients with traumatic loss of consciousness were admitted to the hospital for overnight observation, especially if there was no responsible adult to be with the patient at home. However, changes in managed care over the past several decades and the increased availability of computed tomography have led to a marked decrease in such admissions.[42]

In addition to history and examination, CT has become the mainstay of evaluation, to the exclusion of skull x-ray. Prolonged or deteriorating mental status or the presence of neurologic signs or other risk factors are still clear indications for CT scanning, observation, or both after MTBI. For example, MTBI patients whose GCS scores are 13 or 14 on admission have a much higher incidence (up to 28%) of abnormal findings on CT scanning than do patients with a GCS score of 15.[43] In addition, on rare occasions, even MTBI patients whose initial CT scans are negative may develop surgical complications after discharge; repeat CT scanning should thus be considered in patients who return with severe, persistent symptoms or new neurologic signs.

The diagnosis of contusion is also important for its longer-term prognostic value. Patients with MTBI complicated by cerebral contusion have a 6-month outcome that is more consistent with that of patients with moderate head injury[39] and are thus candidates for more intensive, longer-term observation and management.

In the postacute period, MRI, single-photon emission computed tomography (SPECT), and quantitative EEG can provide additional documentation and localization of brain injury that can be very valuable in guiding nonsurgical management [*see Figure 1*]. For example, MRI can help provide a presumptive diagnosis of diffuse axonal injury and subtle brain contusions that might have been be missed on CT. Standard neuropsychological testing is usually not indicated in the MTBI patient, but some brief, specialized cognitive batteries that have been developed for this population can be very helpful in diagnosis and follow-up. These include the Sideline Assessment of Concussion (SAC) and the Automated Neuropsychological Assessment Metric (ANAM).[28,29,44-46]

### MANAGEMENT OF MTBI

Postconcussive symptoms, which include headache, dizziness, fatigue, and documented deficits in cognition, can be seen even after mild injuries without loss of consciousness. In general, the prognosis for recovery is very good, with most cognitive and somatic sequelae improving markedly by 3 months; 85% of patients experience no disabling symptoms 1 year after injury.[40,47] In the small percentage of patients who have postconcussive complaints and disability over periods exceeding 1 year, psychogenic factors can often contribute to the persistence of symptoms. Patients who have persistent symptoms of anxiety, depression, or both need appropriate diagnosis and treatment, preferably by a psychiatrist who has experience with TBI.

Probably the most important element in the longer-term management of patients with MTBI is the clinician's recognition that the postconcussive symptoms in these patients have a structural cause and that the patients usually recover. Attention deficits and fatigue appear to be especially common and troubling, and there is nothing more disconcerting to the intelligent but symptomatic MTBI patient than to be told by his physician, family, or employer that there is nothing wrong. Early symptomatic management and counseling as to what to expect can help avoid the all too common delayed emotional symptoms of anxiety and depression, especially in patients who may be at risk because of underlying psychopathology. Recognition that the concussed patient is not always able to understand oral counseling in the emergency department has led some physicians to use information booklets that expand and reinforce initial recommendations. Recent controlled studies have convincingly demonstrated that the use of such booklets significantly reduces long-term morbidity, particularly with regard to emotional symptoms.[48]

**Moderate and Severe Head Injury**

INITIAL EVALUATION AND RESUSCITATION

An organized team approach to the acute management of the unconscious patient with TBI is essential and includes prehospital, intensive care unit, and post-ICU care. A cornerstone of early evaluation and care is recognition of deterioration in patient status through the sequential use of a standardized measure such as the GCS score [*see Figure 2*], along with checks of lateralized deficits in neurologic function and careful attention to pupillary responses. The history should be obtained from witnesses, particularly with regard to the onset of coma. For example, if a patient who is comatose had an initial interval of lucidity or semilucidity, an expanding mass lesion may be present, and severe diffuse axonal injury is less likely.[49]

The importance of cardiopulmonary resuscitation in patients with acute TBI cannot be overstated.[50] Airway and shock management should be the first priority in all trauma patients. The loss of cerebrovascular autoregulation places the brain at increased risk for cerebral ischemia from systemic hypotension, and levels of hypercapnia tolerated by the normal brain can lead to critical marginal increases in intracranial pressure (ICP) in the patient with head injury. Most prehospital deaths after TBI are probably caused by vascular and respiratory failure. This is supported by the marked improvements in outcome achieved by emergency care systems with early prehospital intubation and resuscitation.

Shock is usually caused by hemorrhage elsewhere in the body, not in the head. Cerebral perfusion pressure should be maintained above 70 mm Hg by vigorous management of hypotension. Fluid resuscitation with normal saline or lactated Ringer solution is generally recommended, but patients with TBI should not receive excessive hydration, and central venous pressure should be monitored. Glucose administration should be avoided because it has been linked to poor outcome, possibly through increased lactic acidosis.[51]

Comatose patients with TBI are often hypoxic or hypercapnic, even though ventilation may appear to be normal. Patients who are in a coma (i.e., those with a GCS score < 8) should undergo gentle hyperventilation, via intubation if necessary, until a carbon dioxide tension ($P_{CO_2}$) of about 35 mm Hg is achieved. Short-term hyperventilation to levels of about 25 mm Hg can be lifesaving in the patient with impending tentorial herniation. However, the recommended standard is that chronic hyperventilation be maintained at a $P_{CO_2}$ no lower than 25 mm Hg, because lower levels reduce cerebral blood flow and have a negative impact on outcome. Sedation or pharmacologic paralysis should be used when necessary to control acute agitation. The head should be elevated and immobilized in the plane of the body for airway maintenance and facilitation of cranial venous return.

Finally, the special nutritional requirements of the TBI patient also need particular attention, from coma through subacute recovery. Early nutritional support (often parenteral) may be associated with improved survival and decreased disability.[52]

*Radiologic Examination*

CT has revolutionized the diagnosis and management of mass lesions in patients with head trauma; it should be performed in all patients with a GCS score of less than 15 and in those who have focal signs or posttraumatic amnesia. Comatose patients must be accompanied by trained personnel on the way to the CT suite because patients who are assumed to be stabilized may suffer respiratory arrest or irreversible brain damage as a result of simple airway problems en route.

The principal role of CT is in the diagnosis and management of acute surgical lesions. Hemorrhage can occur in the subarachnoid, subdural, epidural, and intraventricular spaces or in the brain parenchyma. Subdural and epidural hematomas should

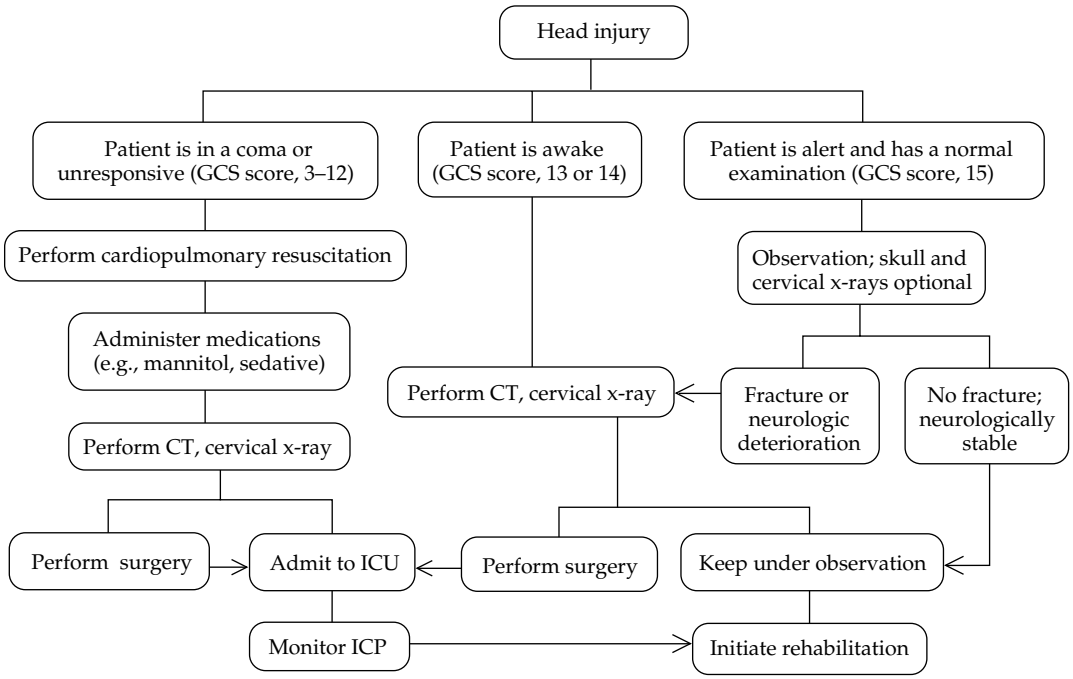


*Figure 2* **Management algorithm for patients with traumatic brain injury. (GCS—Glasgow Coma Scale; ICP—intracranial pressure)**

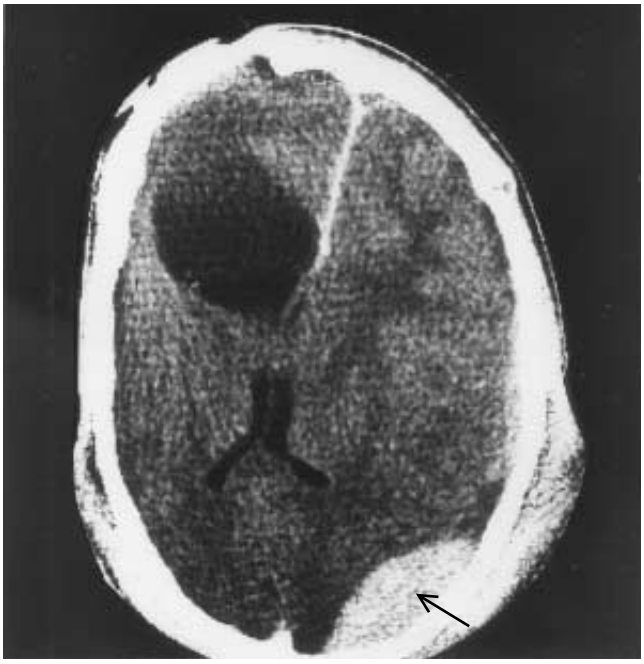

*Figure 3* **CT in a 19-year-old man with a history of head injury and recent occipital injury shows the old lesion, the resulting midline distortion, and an epidural hematoma (arrow) resulting from the recent injury.**

be evacuated promptly when associated with a significant mass effect, because it has been shown that there is a significantly poorer outcome with surgical delays of greater than 4 hours.[53,54] However, surgical management of intraparenchymal hemorrhage will vary, depending on the size, mass effect, location, and neurologic status. Intraventricular hemorrhage will generally require ventricular drainage, and it has also been associated with a worse prognosis. Obliteration of the basilar cisterns from mass effect also portends a worse outcome, as does diffuse hypodensity typical of cerebral hypoxia.[49]

CT has made the skull x-ray all but obsolete, and the latter rarely affects management.[55] Normal findings on initial skull x-ray or CT should not lull the clinician into ignoring the possibility that a delayed hematoma may develop, although this is fortunately relatively rare [*see Figure 3*]. Whether in the hospital or at home with a responsible adult, observation remains a critical element of care, even for patients with MTBI.

MRI promises to be very useful in the long-term management of moderate and severe TBI as well as in the documentation of brain pathology in patients with milder injury. However, it is often impractical and not cost-effective in the acutely comatose patient and is not as good as CT for diagnosis of acute hematomas.

Laboratory tests should include a complete blood count; measurements of electrolytes, glucose, arterial blood gases, and blood alcohol; liver and kidney function tests; and a toxicology screen. In addition, because coagulopathies frequently occur after TBI, other tests may be indicated. Such tests include a platelet count; prothrombin, partial thromboplastin, and thrombin times; and an evaluation of fibrinogen and fibrinogen degradation products.

## ACUTE MANAGEMENT

Acute management of severe head trauma is aimed at minimizing the progression or the effects of secondary injury. Although there are no specific treatments targeting the biochemical events discussed (see above), much progress has been made in early resuscitation and the management of elevated ICP. Evidence-based guidelines and standards for management of patients with severe acute TBI, as well as options for the care of such patients, have been updated by the Joint Section on Neurotrauma and Critical Care and the American Association of Neurological Surgeons, under sponsorship of the Brain Trauma Foundation.[56] These guidelines are also available through the Brain Trauma Foundation Web site (www.braintrauma.org). They represent a major advance in standardization of the management of severe TBI and should be consulted by anyone involved in the care of these patients.

Aspects of care described in the guidelines include early resuscitation; ICP monitoring; ICP treatment threshold and methods; and the use of mannitol, barbiturates, nutrition, hyperventilation, corticosteroids, and prophylactic anticonvulsants. It is important to note that even guidelines that are presented as options for care are very valuable, because such options represent the consensus of experts in areas where studies documenting more definitive levels of certainty are not available or are not possible [*see Table 3*]. The guidelines currently support a standard recommendation against the routine use of aggressive hyperventilation, corticosteroids, and prophylactic anticonvulsants.

### *The Intensive Care Unit, Intracranial Pressure Monitoring, and Cerebral Perfusion Pressure*

After a mass lesion has been surgically treated or excluded, the comatose patient should be managed in the ICU. Preventing secondary insults to the brain remains the principal goal of therapy. In general, the same principles of care that are applied in earlier stages of treatment (see above) are applied at this stage, but better monitoring is available in the ICU. Organization, training, and adherence to relatively simple principles are the mainstay of care.

ICP and cerebral perfusion pressure (CPP) are probably the most sensitive measures for monitoring the patient with severe TBI, and the results of these assessments correlate significantly with outcome.[57-59] The current guideline recommends that ICP be monitored in comatose patients in whom CT yields abnormal results and in those in whom CT is normal but who have two or more of the following risk factors: age greater than 40 years, motor posturing, or a systolic blood pressure of less than 90 mm Hg. The particular monitoring technique to be used is determined by the neurosurgeon and the facilities available. An intraventricular catheter is recommended, because it can also be used for ventricular drainage as needed, though fiberoptic epidural or subdural transducers can also be used.[60]

The current standard measures for control of elevated ICP include sedation, paralysis, controlled hyperventilation, use of mannitol and other osmotics, ventricular drainage, and barbiturate coma [*see Table 4*]; these interventions are usually undertaken in that sequence to maintain an ICP of lower than 20 mm Hg.[58,61] It is recommended as a guideline that mannitol be given in intermittent boluses of 0.25 to 1.0 g/kg every 4 hours as needed, but serum osmolarity should be kept below 320 mOsm/L because of concerns about renal failure. Use of a Foley catheter is strongly recommended to monitor urine output and help maintain euvolemia through adequate fluid replacement. Barbiturate coma significantly improves outcome in patients younger than 45 years with otherwise uncontrolled ICP. This is the last step recommended as a guideline in the nonsurgical control of ICP.

Barbiturate coma is induced with pentobarbital at an initial loading dose of 10 mg/kg I.V. over 30 minutes, and serum levels should then be maintained at 3 to 4 mg/dl with dosages of about 1 mg/kg/hr. The literature supports a standard recommendation that corticosteroids not be used for neuroprotection or control of ICP in patients with severe TBI.[62] Finally, progressive elevations in ICP may be caused by lesions that require surgery, such as delayed hematoma or hydrocephalus. Similarly, seizures, hyponatremia, and airway problems will raise ICP.

### MANAGEMENT OF AGITATION

Patients with TBI often experience agitation during the immediate recovery period. Nonpharmacologic interventions, including limiting environmental stimuli and providing gentle interaction with the patient, are of great importance in early management and should typically be the first line of therapy. When ICU patients require chemical restraint for their own safety and the safety of staff, propofol may be given intravenously to manage agitation; the recovery time with propofol is quicker than with benzodiazepines such as midazolam.

After the patient has left the ICU, benzodiazepines (e.g., lorazepam, 0.5 to 2.0 mg p.o. or I.M., or clonazepam, 0.5 to 2.0 mg p.o.) may be the first choice, either alone or in combination with carbamazepine or valproate. However, benzodiazepines may cause disinhibition in some patients with brain injury. Neuroleptics (e.g., molindone, 10 mg p.o., b.i.d., or haloperidol, 0.5 to 2.5 mg p.o., b.i.d.) are less desirable because they may cause extrapyramidal effects, akathisia (a subjective sense of restlessness that may prolong agitation), or both. Some newer agents, such as olanzapine, 2.5 to 5.0 mg/day orally, may have fewer side ef-

*Table 3* Evidence-Based Guidelines for the Management of Severe Head Injury[62]

| *Subject* | *Certainty Level** | *Recommendations* |
|---|---|---|
| Trauma systems | Guideline | All regions in the United States should have an organized trauma care system |
| Resuscitation | Guideline | Systolic BP < 90 mm Hg or hypoxia must be scrupulously avoided or corrected immediately |
| | Option | Mean arterial pressure should be kept above 90 mm Hg |
| Integration of brain-specific treatments into initial resuscitation | Option | When clear signs of transtentorial herniation are present, the herniation should be treated aggressively; hyperventilation should be performed rapidly (mannitol is desirable with adequate volume resuscitation); sedation and short-acting neuromuscular blockade can be used but may interfere with the neurologic examination |
| ICP monitoring | Guideline | Admission GCS 3–8 plus abnormal CT scan, *or* GCS 3–8 and normal CT plus age > 40 years, *or* motor posturing, *or* systolic BP < 90 mm Hg |
| ICP treatment threshold | Guideline | ICP > 20–25 mm Hg |
| | Option | ICP treatment should be corroborated by frequent clinical examination and cerebral perfusion pressure data |
| ICP treatment critical pathway | Option | [*See* text, Table 4, and reference 47] |
| CPP | Option | Maintain CPP above 70 mm Hg |
| Hyperventilation | Standard | In the absence of increased ICP, chronic prolonged hyperventilation ($P_aco_2$ < 25 mm Hg) should be avoided |
| | Guideline | Prophylactic hyperventilation ($P_aco_2$ < 35 mm Hg) should be avoided during the first 24 hr after severe TBI because it can compromise CPP when cerebral blood flow is reduced |
| | Option | Hyperventilation therapy may be necessary for brief periods when there is neurologic deterioration or when ICP elevations are refractory to other treatment |
| Mannitol | Guideline | Mannitol is effective for ICP control; intermittent boluses (0.25 to 1.0 g/kg) may be more effective than continuous infusion |
| | Options | Indications for mannitol before ICP monitoring are progressive neurologic deterioration or transtentorial herniation not attributable to systemic pathology |
| | | Maintain serum osmolality < 320 mOsm |
| | | Maintain euvolemia by adequate fluid replacement; use Foley catheter |
| Barbiturates | Guideline | High-dose barbiturates may be used in hemodynamically stable severe TBI patients with ICP elevations refractory to maximal medical and surgical therapy |
| Glucocorticoids | Standard | Glucocorticoids are not recommended for ICP control or improving outcome in severe TBI patients |
| Nutritional support | Guideline | Replace 140% of resting metabolic expenditure (100% in paralyzed patients) by using enteral or parenteral formulas, with at least 15% of calories as protein |
| | Option | Feeding by gastrojejunostomy is preferred |
| Antiseizure prophylaxis | Standard | Prophylactic use of phenytoin, carbamazepine, or phenobarbital is not recommended for preventing late posttraumatic seizures |
| | Option | Short-term (1 wk) phenytoin or carbamazepine is recommended to prevent early posttraumatic seizures in high-risk patients after head injury |

*Note:* This table should not be used alone as a guide to therapy. Clinicians are referred to the full guideline document (see text).
*For determining certainty level, studies that are controlled and randomized rank highest, and expert opinion ranks lowest. The highest level of certainty is represented by standards; the next highest, by guidelines; and the lowest, by options for care.
BP—blood pressure CPP—cerebral perfusion pressure GCS—Glasgow Coma Scale ICP—intracranial pressure $P_aco_2$—arterial carbon dioxide tension TBI—traumatic brain injury

*Table 4* Management of Intracranial Pressure

| *Treatment* | *Dosage* |
|---|---|
| Sedation (with morphine) | As needed |
| Paralysis (with pancuronium) | As needed |
| Ventricular drainage | As needed |
| Mannitol | 0.25–1.0 g/kg q. 4 hr |
| Hyperventilation | To a $Pco_2$ of 35 mm Hg (25 mm Hg only for brief periods, if needed for transtentorial herniation) |
| Barbiturate coma (pentobarbital) | Loading dose of 10 mg/kg, then 1 mg/kg/hr |

$Pco_2$—carbon dioxide tension

fects. Animal models suggest that neuroleptics have a negative long-term effect on recovery.[63] Dopamine agonists such as amantadine and bromocriptine have also been successfully used for postcoma agitation caused by impairment of dopaminergic and other ascending monoaminergic pathways.

A recent survey of rehabilitation physicians suggests that those who are more experienced in caring for patients with brain injury tend to use carbamazepine and beta blockers in preference to neuroleptics for management of agitation. In all cases of prolonged confusion or agitation, however, other causes must also be considered, such as the side effects of medication, infection, electrolyte imbalance, hypoxia, and late intracranial complications.

### TREATMENT OF NEUROPSYCHIATRIC SEQUELAE

The neuropsychiatric sequelae of brain injury, both socially and in the workplace, are well appreciated. Verbalizations and behavior can be striking, especially when the patient has a reduced ability to self-monitor and is unconcerned.[64,65] Neurologic abnormalities may not be as distressing to the patient and his or her family as personality changes and inappropriate behavior. Suitable treatment of neurobehavioral sequelae will often decrease patient and caregiver distress and markedly improve overall outcome.[66]

Intellectual impairments increase as the duration of posttraumatic amnesia rises from less than 1 hour to longer than 7 days. Inappropriate behavior associated with frontal, temporal, and limbic connections (e.g., poor social judgment, increased irritability, and poor impulse control) is particularly common, even in patients in whom imaging studies show no focal pathology. Frontal-thalamic reticular circuit damage may also cause fatigue and frequent sleep disturbances.

#### *Depression*

Studies consistently show a 25% to 50% incidence of depression after TBI. In one study, of the 75% of TBI patients who were not depressed at the initial interview, 25% developed depression during the first year of follow-up; the mean duration of depression was 4 to 5 months for the total sample.[67] Patients frequently complain of hopelessness, a loss of interest in usual activities, self-deprecation, a lack of energy, and a lack of self-confidence. Anxiety symptoms may be prominent, especially within 6 months after injury.

Many reports suggest that the depression associated with stroke and TBI has a neurologic basis. Acutely depressed patients with TBI frequently have left anterior lesions, whereas patients with mixed anxiety and depression are more likely to have right-hemisphere lesions, a longer duration of depression, and poorer psychosocial outcome.[67] The incidence of depression, its duration, and its associated symptoms, such as anxiety, may therefore be related to the location and laterality of cerebral pathology.

Antidepressants are indicated in the treatment of depression and of mixed anxiety and depression in TBI [*see 13:VIII Anxiety Disorders*]. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, and paroxetine are favored because they are safe and easy to administer and do not cause unwanted anticholinergic side effects. Tricyclic antidepressants may also be used; desipramine and nortriptyline have the fewest anticholinergic and antihistaminic properties. The antidepressant venlafaxine is both serotoninergic and dopaminergic. Although stimulants such as methylphenidate and dextroamphetamine have primarily been used in TBI patients to treat attention difficulties, they can also be used to treat depression or to augment antidepressant treatment with SSRIs or tricyclic antidepressants. Bupropion should be given only with caution to patients with brain injury, because it can lower the seizure threshold.

#### *Anxiety*

Anxiety disorders, alone or in combination with depression, occur in patients with TBI and are treated with SSRIs, tricyclic antidepressants, benzodiazepines, or buspirone. As with antidepressants, buspirone has a 2- to 3-week latency period until it reaches full therapeutic effect. Patients with phobic avoidance are best treated with a combination of cognitive-behavioral therapy and benzodiazepines. Symptoms of posttraumatic stress disorder (PTSD) may occur and are more common in patients with MTBI than in patients with more severe TBI. Longer periods of posttraumatic amnesia, in which an explicit memory of the upsetting events is not established, may protect against the development of nightmares and intrusive thoughts about the trauma.[68] The development of PTSD symptoms probably entails implicit memory by a mechanism similar to negative conditioning and thus may not require explicit memory of the event.[69]

#### *Irritability and Aggression*

Irritability occurs in more than 50% of patients with moderate or severe traumatic head injury during the first 6 months after injury. Aggressive outbursts in brain-injured patients tend to be verbal and brief and are precipitated by seemingly trivial provocations. Patients may be remorseful and apologetic afterward but seem to be unable to curtail subsequent outbursts. Irritability and aggression may occur in patients without a history of such behavior; disinhibition caused by frontal system dysfunction and possible injury to limbic and hypothalamic structures is implicated.[70] Impaired serotonin transmission may also be involved, because low levels of 5-hydroxyindoleacetic acid (5-HIAA) have been noted in the cerebrospinal fluid of impulsive, violent patients. Anticonvulsants, lithium, buspirone, beta blockers, SSRIs, and stimulants have been variously reported to be of use in decreasing the amount of aggression.[71]

#### *Attention Deficits*

The stimulants dextroamphetamine and methylphenidate may improve attention and concentration and are often used in the clinic in selected patients. A randomized, controlled study of methylphenidate in adults with moderate TBI found a more

rapid rate of recovery of attention and improved scores on motor and disability tests but no change in ultimate overall outcome through the use of methylphenidate.[72] Findings of a recent controlled crossover study on the use of methylphenidate in children suggested that there is no difference in behavior, attention, memory, or processing speed between persons receiving medication and those given placebo.[73] Clear guidelines on the use of stimulants to treat attention deficits in TBI await additional studies.

#### TREATMENT OF POSTTRAUMATIC EPILEPSY

The risk of epilepsy in patients with closed-head injury is relatively small: 2% to 5% in all patients and about 10% to 20% in patients with severe closed-head injury.[74] Some studies have shown a higher incidence of seizures in patients with depressed skull fractures (15%), hematomas (31%), and penetrating brain wounds (50%).[75,76] In all cases, the risk decreases markedly with time. Although the relative risk of developing epilepsy 10 to 15 years after penetrating head injury is still 25 times higher than in the normal age-matched population, 95% of patients with penetrating head injury will remain seizure-free if they have no seizures during the first 3 years after injury.[77]

Because most patients who develop posttraumatic epilepsy in the first week after injury will have recurrent seizures for some time, anticonvulsant therapy is indicated in documented cases.[78] Controlled, randomized studies have shown that the use of phenytoin, phenobarbital, carbamazepine, or valproate does not prevent the development of posttraumatic epilepsy beyond the first week after injury. It is now recommended as a standard of care that these medications not be used to prevent posttraumatic epilepsy in patients who have not had a seizure.[79] In light of the sensitivity of the acutely traumatized brain to the secondary insult of a grand mal seizure, I recommend routine short-term use (for 1 to 2 weeks after injury) of phenytoin or carbamazepine in high-risk patients with acute TBI. Carbamazepine may be preferable because it helps control agitation in some patients.

Evidence suggests that iron-catalyzed lipid peroxidation may partly mediate the development of posttraumatic epilepsy; inhibitors of lipid peroxidation, such as methylprednisolone and α-tocopherol, can prevent iron-induced epilepsy in animals, but no well-controlled clinical trials have explored this avenue.[80]

### Long-term Outcome

The young-adult brain has a remarkable capacity to compensate for many aspects of injury naturally. Although disabilities such as hemiparesis, seizures, and certain language disorders may initially appear more dramatic, the most devastating long-term impairments are the cognitive defects, attention deficits, and, in particular, behavioral changes that often persist after TBI.[81]

Prognosis for full recovery must be more guarded in the elderly, who have been reported to have about twice the mortality of younger TBI patients. Likewise, seemingly less severe injuries often result in worse functional outcomes in older patients.[82]

Measurement of outcome from TBI remains a challenge. Functional measurement instruments include the Glasgow Outcome Score, the Disability Rating Scale, the Rancho Los Amigos Score, the Functional Independence Measure, and various neuropsychological, behavioral, and quality-of-life measures. However, return to gainful employment is probably the best overall measure of long-term outcome.[83] About 50% of patients who survive severe TBI eventually return to work. In recent studies, return to work was also the single best correlate of perceived quality of life.[84,85]

Accurate predictors of outcome are also important to patients, their families, and caregivers in understanding recovery and planning for care. Early predictors of good outcome include a higher preinjury intelligence, youth, and a lower severity of injury.[49] Certain genotypes, such as the *ApoE4* allele, may affect recovery and outcome.[86,87] In a large multidisciplinary study of survivors of penetrating head injury, the presence of seven factors were significantly predictive of unemployment: hemiparesis, epilepsy, visual field loss, verbal memory loss, visual memory loss, psychological problems, and violent behavior. These factors represent different domains of brain function and were relatively equipotent in the model (i.e., it was the number of impaired domains, not impairment in any one particular domain, that was predictive of unemployment). The brain may thus compensate for injury by utilizing whichever functional domains are still available to it.[88]

### Traumatic Brain Injury Rehabilitation

In the 1990s, the field of TBI rehabilitation blossomed. A profusion of therapies, including coma stimulation, cognitive rehabilitation, speech therapy, occupational therapy, and recreational therapy, are now available. Their use is largely empirical, and these sometimes expensive interventions have not been subjected to a high level of scientific scrutiny for efficacy and cost-effectiveness. Nevertheless, a growing body of animal and clinical literature supports the beneficial effects of training on the brain and on performance after injury.

The goals of therapy should be recovery of the patient's independence and his or her reintegration into the community. The prevention of maladaptive behaviors is an important secondary goal. However, patients with scarce economic resources can find those resources depleted in the early phases of recovery by the evaluation of and therapy for specific neurologic or cognitive deficits that may resolve even without therapy or may ultimately be of marginal importance to the patient's achieving the goal of independence. Interventions that may be more cost-effective, such as training in decision-making or other community reintegration skills and certain forms of behavioral management, may ultimately be omitted for lack of resources.

Although there is consensus about the benefits of some forms of rehabilitation for patients with TBI, the type, intensity, and duration of rehabilitation that are best for a given patient remain hotly debated.[89,90] For example, a recent large prospective, randomized, controlled trial compared an intensive in-hospital program of cognitive rehabilitation with a limited (and much less expensive) home rehabilitation program in soldiers recovering from moderate to severe TBI.[91] At 1 year after injury, there was no difference between the two groups with regard to return to work, fitness for military duty, or behavioral, neuropsychological, or quality-of-life measures. However, in a subset analysis of patients who were unconscious for longer than 1 hour after suffering TBI, there was a higher return-to-work rate for the patients who underwent hospital rehabilitation than for those who underwent home rehabilitation, suggesting the differential value of these approaches for selected patients. Thus, a fundamental challenge for rehabilitation is to distinguish the effect of the brain's natural processes of recovery from the effects of treatment in patients with varying prognostic risk factors for long-term function. Clear

resolution of these issues will require further properly designed, prospective, controlled, randomized trials.

### Additional Information

Additional information on TBI can be obtained from the American Academy of Neurology (http://www.aan.com), the Brain Injury Association (http://www.biausa.org), and the Brain Trauma Foundation (http://www.braintrauma.org).

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*The author has no commercial relationships with manufacturers of products or providers of services discussed in this subsection.*

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Figure 1 Positron-emission tomography scan courtesy of Dr. J. C. Umhau, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland.

Figure 2 Marcia Kammerer.