Chapter 13

BEHAVIORAL CONSEQUENCES OF TRAUMATIC BRAIN INJURY

EDWIN A. WEINSTEIN, M.D.[*]; ANDRES M. SALAZAR, M.D.[†]; AND FRANKLIN D. JONES, M.D., F.A.P.A. [‡]

[*]*Consultant in Neurology, National Naval Medical Center, Bethesda, Maryland; Consultant in Psychiatry, Walter Reed Army Medical Center, Washington, D.C.; Formerly Chief, Fifth Army Neuropsychiatric Center (World War II)*

[†]*Colonel, Medical Corps, U.S. Army; Professor of Neurology, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Director, Defense and Veterans Head Injury Program*

[‡]*Colonel (ret), Medical Corps, U.S. Army; Clinical Professor, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Past President and Secretary and current Honorary President of the Military Section, World Psychiatric Association; formerly Psychiatry and Neurology Consultant, Office of The Surgeon General, U.S. Army*

John O. Wehrle *Purple Heart* 1966

John O. Wehrle depicts a serviceman in Vietnam who has received his Purple Heart in a Surgical Intensive Care Unit. In combat settings, traumatic brain injury often occurs in conjunction with other injuries, as shown in this painting.

Art: Courtesy of US Center of Military History, Washington, DC.

INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of death and disability in young adult Americans today.[1] The incidence of TBI requiring hospitalization is approximately 200/100,000/y; about 75,000 persons die and another 75,000 are permanently disabled each year. Similarly, in the Vietnam conflict, head and neck wounds accounted for 40% of all battlefield fatalities, and for about 11% of all surviving casualties. Yet, largely because it affects the young and can result in prolonged convalescence and a lifetime loss of earnings, the impact of TBI is greater than most other injuries. The total peacetime economic cost of TBI in the United States has been estimated at over $25 billion per year.

A number of underlying themes will be emphasized in the following discussion of TBI, particularly as a basis for understanding its neuropsychiatric consequences. First, it must be recognized that TBI represents a spectrum of disorders, with regard to mechanism of injury (penetrating vs closed-head injury), severity of injury, and pathology (see below). Secondly, TBI is a dynamic process. The acute evolution of secondary cellular injury and brain swelling in the first hours posttrauma offers a therapeutic window of opportunity that is the subject of intense study and rapid development in the field at present. Postacutely, the natural history of TBI is one of recovery, often to a remarkable degree in young adults. However, this recovery often represents compensation for functions lost, and its pace should not lull health care providers into ignoring the long-term behavioral deficits and maladaptations commonly seen in these patients. Third, "outcome" should be considered a summation of a variety of factors, including not only physical and cognitive recovery but behavioral and psychosocial reintegration as well. Fourth, preinjury status is a major determinant of final outcome after TBI; this has been reemphasized in a recent study showing that preinjury intelligence was the single most important determinant of cognitive performance in a large cohort of head-injured Vietnam veterans.[2] In this chapter, the current understanding of the pathogenesis of TBI will be briefly reviewed, with some comments on experimental treatment. The phenomenology and the cognitive, neurobehavioral, and psychosocial outcome of head injury will be discussed, as will be the behavioral and pharmacological aspects of therapy.

PATHOGENESIS

Closed-head Injury

Given that TBI results in a spectrum of pathologies, all of which can affect outcome, it is relevant to review the various components here. Over the past decades there has been movement from conceptualizing the pathology of closed-head injury (CHI) in terms of hematomas and "coup-contrecoup" contusions to a four-component classification.[3] Three parallel components were initially identified: (1) focal injury, (2) diffuse axonal injury (DAI), and (3) superimposed hypoxia or ischemia. More recently, (4) diffuse microvascular injury with loss of autoregulation has been implicated as playing an important role in the acute stage of moderate and severe head injury. All of these pathological features have been reproduced in animal models of angular acceleration without impact; and possibly except for diffuse axonal injury, all are also features of penetrating head injury (PHI).[4]

Focal Injury

Focal tissue disruption, swelling, contusions, or hematomas at the site of impact or penetration result in focal cortical neurologic deficits referable to that area (eg, aphasia, hemiparesis). By far the most common location for contusions after deceleration injury is in the orbitofrontal and anterior temporal lobes, where the brain lies next to bony edges. This is also an area rich in limbic connections governing mood, emotions, and memory. Thus, a relatively typical pathological picture is often seen in most closed-head injuries (CHIs). Among its most troubling clinical sequelae are attentional, memory, and behavioral abnormalities, which may be referable to the frontal and temporal lobe injury. Subdural hematomas are most common with rapid decelerations such as occur with impact after a fall, especially in the aged, and are usually due to rupture of bridging veins; they appear to be much less

common after penetrating head injury. Delays longer than 4 hours in the surgical management of hematomas appear to worsen prognosis significantly. Delayed hematomas as well as bleeding into contusions are particularly important in the so-called "talk and die" patient, who may initially appear to be at low risk but then deteriorates unexpectedly.[5]

Diffuse Axonal Injury

Diffuse axonal injury (DAI) is one of the most important causes of prolonged coma and persistent severe neurological deficit in CHI. Originally described as a "shearing" injury of axons, it was characterized by axonal "retraction" balls microscopically in the hemispheric white matter, corpus callosum, and brain stem.[6,7] Recent work with mild to moderate fluid-percussion injury in animal models, however, shows that the typical light microscopic histopathology of DAI showing axonal shear may not emerge until 12 to 24 hours postinjury. The only early abnormality is a relatively subtle focal intraaxonal disruption seen on electron microscopy, with an intact axon sheath. This leads to a disturbance of axonal flow, accumulation of transport material with axonal ballooning proximal to the injury, and then eventual delayed severing of axons 12 to 24 hours later.[8,9] The role of alterations in calcium metabolism at the injured site on the axon may be particularly important. One obvious clinical implication of these findings is that *there may be a potential 12 to 24 hour window of therapeutic opportunity* postinjury during which future treatments may prevent total axonal disruption. Another important conclusion is that DAI can be demonstrated even after "minor" head injury, and occurs even in the absence of morphopathologic change in any other vascular, neural, or glial elements. This confirms earlier uncontrolled pathological studies in humans and makes such axonal damage a possible organic basis for the "postconcussion syndrome" and perhaps for the cumulative effects of repeated concussion, as seen in some boxers.[10]

Interestingly, a major feature of the pathology of *dementia pugilistica* is the presence of neurofibrillary tangles (NFT). NFT in Alzheimer's disease and in other conditions such as Guamanian amyotrophic lateral sclerosis, have been postulated to result from abnormalities in axonal flow, in the latter case probably related to aberrant calcium metabolism.[11] While classical Alzheimer plaques are not seen in this condition, recent studies show plaquelike structures that stain with monoclonal antibody to the beta amyloid precursor protein both chronically in boxers and acutely after severe head injury.[12–14] It is unknown whether repeated trauma might alter the secretion, metabolism, or structure of the amyloid precursor protein in such a way as to lead to plaque and NFT formation or whether the phenomenon of lipid peroxidation, which is discussed further in this chapter, may also play a role in this process.

Hypoxia-Ischemia

The classical pathology of hypoxia-ischemia, involving mainly the hippocampus and the vascular border zones of the brain, is frequently superimposed on the other pathological features that are more specific for TBI. The traumatized brain is particularly sensitive to hypoxia-ischemia.[15] When present, such pathology, including the concomitant hippocampal necrosis, can obviously become a major determinant of ultimate clinical outcome, particularly with regard to post-traumatic memory disorders. Recent improvements in the survival of the TBI patient have largely resulted from recognition of the importance of this component and its prevention, especially through the development of emergency resuscitation and transport systems.

Microvascular Change

Diffuse microvascular damage has also been recently implicated as a major component of both closed and penetrating TBI. Depending on the severity of the trauma, early physiological changes include an early loss of cerebrovascular autoregulation with a decreased response to changes in CO_2 and perfusion pressure, and an initial transient systemic hypertension (probably related to release of catecholamines).[16,17] The loss of autoregulation makes the brain particularly susceptible to fluctuations in systemic blood pressure. For example, systemic hypertension can increase the risk of vascular dilatation with hyperemia and brain swelling, or otherwise tolerable hypotension can result in ischemic damage. In addition, altered vascular sensitivity to circulating catecholamines or acetylcholine can lead to vasoconstriction and further focal ischemia or reperfusion injury ("no-reflow" phenomenon). Recent blood flow studies have confirmed a relative cerebral ischemia in a large proportion of TBI patients acutely.[18] Such changes may be susceptible to pharmacological interventions.

The pathology appears to be biphasic, with an early, transient alteration of the blood-brain barrier (BBB), and a more delayed (6 plus h) endothelial change.[19,20] Diffuse perivascular damage with astrocytic footplate swelling is a prominent feature at both the light and electron microscopic levels within minutes of high-velocity gunshot wounds as well as after acceleration injury in nonhuman primates. The basic cause of this swelling was initially thought to be a break in the endothelial BBB, but recent studies have demonstrated an increased pinocytotic transfer of horseradish peroxidase marker with intact endothelial tight junctions.[21] The astrocytic swelling is usually maximal at 30 to 60 minutes and is much reduced by 6 hours postinjury; it is thought to represent an initial reaction to the altered transport across the BBB. It should be emphasized, however, that the classic concept of BBB breakdown and cerebral edema post-TBI is undergoing radical revision, particularly in the absence of evidence for increased brain water after either uncomplicated PHI or CHI.[22] Cerebral edema, per se, may become more of a factor when hypoxia, ischemia, or both complicate the injury.

The second microvascular phase is one of endothelial change, including formation of intraluminal microvilli or blebs, which then break to form endothelial craters. This peaks at about 6 hours postinjury but usually persists as long as 6 days. Although the clinical significance of these changes is still not known, they are probably related to the altered microvascular sensitivity to circulating neurotransmitters, to the loss of autoregulation, and perhaps to secondary brain swelling. Recent studies have shown an associated loss or inhibition of various endothelial hormones including endothelium-derived relaxing factor (EDRF).

EDRF was first described almost a decade ago and has recently been identified as nitric oxide.[23] Inhibition of EDRF may be responsible for prolonged vasoconstriction and perhaps the so-called "no reflow" phenomenon leading to secondary focal ischemia, while loss of other factors may have the opposite effect. One of the principal inhibitors of EDRF in TBI appears to be the superoxide radical, which has also been shown to have a vasoconstrictive effect in experimental models.[24,25]

Application of free radical generators (such as xanthine-xanthine oxidase) to the intact pial surface of nontraumatized animals reproduces very similar changes to those seen after TBI.[26,27] Superoxide dismutase will prevent or reverse this vascular hyperactivity experimentally, suggesting that the vasoconstrictive effect is mediated through the superoxide radical itself.

Secondary Tissue Injury

The picture of a TBI patient who is initially relatively stable and awake or in light coma and then deteriorates and dies is all too common. While some of these cases represent delayed hematoma amenable to surgery, most are probably related to an uncontrolled brain swelling that does not respond to conventional management. Over the past decade, delayed secondary injury at the cellular level has come to be recognized as a major contributor to this phenomenon and to the ultimate tissue loss after TBI.

Understanding of the pathogenesis of secondary injury is thus particularly important to the present-day management of the head-injured patient. As suggested above, a cascade of biochemical and physiological events is set in motion in injured tissue. This includes changes in arachidonic acid metabolites such as the prostaglandins and the leukotrienes,[28] the formation of oxygen free radicals,[16] changes in neuropeptides,[29] electrolytes such as calcium and magnesium,[30] neurotransmitters such as glutamate or acetylcholine,[31,32] lactic acid,[33] various kinins, and a leukocyte response with release of lymphokines such as interleukin-1.[34]

These products can result in progressive secondary injury to otherwise viable brain tissue through a number of mechanisms: (*a*) by altering vascular reactivity and producing further ischemia, (*b*) by producing brain swelling (hyperemia, edema, or both), (*c*) by injuring neurons and glia directly or activating macrophages that result in such injury, or (*d*) by establishing conditions favorable to secondary infection. In other words, much of the ultimate brain loss after PHI may be due not to the injury itself, but to an uncontrolled vicious cycle of biochemical events set in motion by the trauma.

Oxygen Free Radicals and Lipid Peroxidation

Perhaps the most important path of cellular injury in TBI involves oxygen free radicals. These are produced early in ischemic and traumatic tissue injury, both in the central nervous system and elsewhere.[16,35,36] The superoxide radical ($O_2^-\bullet$) is formed through a variety of mechanisms, including normal mitochondrial respiration, the xanthine oxidase and arachidonic acid pathways, or by activated leuko-

cytes. The phenomenon of receptor-mediated phospholipase activation may play an important role in the initial release of arachidonic acid after both trauma and ischemia.

The superoxide radical results in tissue injury in its own right through its effect on the microvasculature. However, when combined with its own metabolite, hydrogen peroxide, in the presence of free iron, it forms the hydroxyl radical (OH•). This reacts with the abundant lipids in the brain in the process of lipid peroxidation, with further release of arachidonic acid and a vicious cycle in which more free radicals are produced through the cyclooxygenase pathway (along with prostaglandins), overwhelming natural free radical scavenging mechanisms. There is a marked rise in lipid peroxidation markers as early as 2 hours postinjury, and lasting at least 5 days in severely head-injured patients. This confirms the ongoing nature of delayed secondary cellular injury in the postacute period, as well as the possibility that the postinjury therapeutic window of opportunity may be considerably longer than has been thought until now.[37]

Pharmacological intervention to reduce the formation of free radicals, or to scavenge those already formed, or both would thus be expected to reduce ultimate tissue injury. Animal models have confirmed this potential benefit in several systems. Because free radicals are formed through a number of biochemical pathways, a variety of drugs or drug combinations may be useful to control them. These include the use of steroids to inhibit lipid peroxidation and the release of arachidonate (megadose methylprednisolone and especially the nonglucocorticoid 21-aminosteroids or "lazaroids");[38] α-tocopherol (Vitamin E) and its analogues;[39,40] cyclooxygenase inhibitors to block prostaglandin formation; xanthine oxidase inhibitors such as allopurinol;[41,42] iron chelators such as desferrioxamine;[43] enzymes such as superoxide dismutase and catalase;[27,44] and various other free radical scavengers such as mannitol and dimethyl sulfoxide.

Superoxide dismutase (SOD) may be particularly attractive as therapy because it scavenges all superoxide radicals regardless of their source. In a particularly relevant model using intracranial balloons in dogs to mimic subdural hematoma, SOD in doses equivalent to those being used in current clinical pilot trials practically eliminated BBB breakdown and postdecompression pathological change when compared to conventional therapies, and decreased mortality from 80% to 0%.[44] Clinical pilot studies have shown a 50% decrease in mortality in severely head-injured patients treated with SOD, but final conclusions must await a larger controlled study.[45]

Penetrating Brain Injury

The majority of casualties with penetrating head wounds who survive long enough to reach the hospital level have been injured by fragments from an explosive munitions.[46] Penetrating wounds, as noted, share a number of the features of moderate and severe closed-head injuries. These include the frequent involvement of more than one lobe; contusions, hematomas, and hemorrhages, some distant from the point of penetration; edema; hypoxia, ischemia, or both; and diffuse microvascular injury with loss of auto-regulation. There are, however, some important clinical differences.

Whereas the soldier with a moderate or severe acceleration/deceleration closed-head injury is by definition unconscious, and the severity of the injury can be graded by the Glasgow Coma Scale, a slight majority of the men who suffered a penetrating head injury in Vietnam did not lose consciousness, or did so only briefly. Of 342 subjects in the Vietnam Head Injuries Study, 53% had no or only momentary unconsciousness, and only 15% had prolonged unconsciousness.[47] While retrograde and anterograde amnesia are almost invariably present in moderate and severe closed-head injury, 121 of the 342 patients in the Vietnam study reported having had no amnesia. Penetrating head injuries have a much higher incidence of seizures with figures up to 50%. The rate in closed-head injuries in which the dura mater has not been pierced runs from 2% to 11% depending on the complications.

The neurological deficits following penetrating brain injuries are more focal and variable, depending, as most do, on the particular cortical area involved. The deficits include aphasia, hemiplegia, and hemiparesis; cortical sensory disturbances; visual field defects; and impairments in visuospatial processing. Closed-head injury patients with damage to frontal and temporal limbic structures are more apt to manifest long periods of disturbed consciousness and impairments of memory, attention, personality, perception of reality, and social behavior. These differences are not absolute. Patients with closed-head injuries may have focal signs depending on the point of impact, and penetrating injuries of the basilar and other deep structures can result in prolonged unconsciousness and memory loss.[47]

POST-TRAUMATIC STRESS DISORDER

The potential interaction between traumatic brain injury and post-traumatic stress disorder (PTSD) remains unclear. The second author has had the opportunity to address this issue in a large cohort of head-injured Vietnam veterans and a group of uninjured Vietnam combat veteran controls participating in the Vietnam Head Injury Study.[48] The data indicate that 15% of head injured and 8% of controls fit the criteria previously established for post-traumatic stress disorder in non-brain-injured subjects on the Minnesota Multiphasic Personality Inventory.[49] Neither total brain volume loss, nor lesion location, nor post-injury cognitive change showed a relationship with PTSD scores.

Head-injured PTSD subjects reported relatively decreased psychological support from community and government upon their return from the Vietnam theater, whereas control PTSD subjects complained more often of a general negative impact of the war on their lives. As expected, PTSD correlated with other measures of psychopathology, especially depression, in both controls and head-injured men. The findings suggest that while many factors may contribute to the development of PTSD, the brain injury itself may play a less important role than other psychological variables. Treatment of PTSD is addressed in Chapter 16, Chronic Post-Traumatic Stress Disorders.

MILD HEAD INJURY

Mild head injury (concussion) has been defined as an acceleration/deceleration closed-head injury, almost always associated with a period of amnesia, usually with a momentary interruption of, or brief change in, consciousness, and followed by a characteristic group of symptoms, including headache, dizziness, poor memory and concentration, fatigue, and irritability.[50] The injuries are incurred mainly as the result of motor vehicle injuries, assaults and falls.

The term concussion has been largely replaced by the designation mild or minor head injury because over the past 20 years it has been shown that such injuries may be associated with neuroanatomical and neurophysiological abnormalities, and with deficits in neuropsychological tests. Concussion, on the other hand, had been thought to involve a shaking up of the contents of the skull without any structural lesions. Animal models of concussion, however, have shown diffuse axonal damage, and magnetic resonance imaging (MRI) as well as positron emission tomography (PET) and power-spectral electroencephalogram (EEG) have repeatedly demonstrated structural, metabolic, and functional changes in humans with mild head injury.

Neuropsychological tests have shown impairment in sustained attention, delayed memory, and impaired ability to process multiple items of information simultaneously.[51,52] Such deficits usually clear over a 3-month period in patients without a history of previous head injury or drug abuse.[53]

These and other data indicate that the post-concussion syndrome cannot be explained solely on a psychological basis, as the result of emotional trauma, and a desire for legal compensation. The symptoms appear in the great majority of patients who have sustained mild head injuries. They occur frequently following sports-related injuries, in which case the motivation to return to athletic competition is high.[54] The symptoms of patients seeking legal redress may clear before settlement[55] and a lump sum award does not necessarily cure the condition.[56]

There are a number of reasons, however, why the symptoms cannot be accounted for on a traditional lesion deficit model, and why psychological and social factors are relevant. The severity of the brain injury as measured by the duration of the period of unconsciousness and the length of the post-traumatic amnesia does not correlate with the number and intensity of such symptoms as headaches, difficulty in concentration, irritability, noise sensitivity, and fatigue.[57] Even though test scores return to normal, and MRI abnormalities (if they have been present) clear, symptoms may persist.

The early symptoms that appear immediately or shortly after the injury, such as headache, dizziness, drowsiness, nausea, and blurred vision are thought to be a direct result of the brain injury. Later manifestations that come on a few weeks after injury include difficulties in memory (aside from the retrograde amnesia [RA] of which patients seldom complain) and concentration, fatigue, insomnia, irritability, noise sensitivity, and depression that can be regarded as responses to the stresses of the patient's cognitive and attentional deficits, and their anticipated consequences.

The persistence of headaches and dizziness or vertigo in the absence of signs of vestibular dysfunction indicates an association with anxiety or depression.

Despite the trauma, the patient is in some respects under less stress in the period immediately following the accident. He is likely to have been relieved that his injury was not serious, and to have been assured that he will recover completely. There is more stress when he returns to work and finds that his mental capabilities are reduced. The increased effort required causes fatigue, and he may become anxious and depressed. He may face the skepticism and disapproval of those who believe that he should have recovered from an apparently minor injury. These features are highly relevant to treatment.

The overall aim of treatment is the prevention of a secondary traumatic neurosis. If there is evidence of brain damage, the patient should be so informed. There is nothing more frustrating for the conscientious, intelligent patient than to be told that there is "nothing wrong" with him, a statement that suggests that he is malingering or not trying. Fatigue is the most troubling symptom interfering with return to work. The relationship of fatigue to diminished mental capacity and stress should be discussed with the patient and his supervisors. To control the situation, a graded work schedule should be instituted so that the patient can work within the limits imposed by his fatigue. Periodic neuropsychological testing may help to monitor progress.[58] A graded return to full workload over a period of 4 to 8 weeks is suggested.

MODERATE AND SEVERE HEAD INJURY

The severity of a head injury is evaluated by the findings on computed tomography (CT) and MRI scans, the depth of coma, the duration of the loss of consciousness, and the length of the anterograde amnesia (AA). Degrees of severity are differentiated as follows:

- Moderate and severe TBI lesions include contusions, hemorrhages, and hematomas, which are rare in mild head injury.
- Mild head injuries have scores of 13 to 15 on the Glasgow Coma Scale on which verbal, ocular, and motor responses are graded, while moderate head injuries score between 9 and 13, and severe head injuries place below 9.
- The loss of consciousness in moderate and severe TBIs is measured in hours and days, rather than in seconds and minutes as in mild head injuries.
- The AA in mild head injury is usually a matter of seconds or minutes, whereas in moderate and severe brain injuries there is an AA of days and weeks. Severe head injuries have an AA of 7 days or more. Whereas mild head injuries may have a momentary RA or none at all, more severe head injuries may have an RA of days, weeks, or months.

Patients recovering from more severe brain injuries with loss of consciousness usually go through several variable stages:

- A period of coma.
- A period of agitation, restlessness, overreaction to stimuli, combativeness, and rambling incoherent speech. Hallucinations may be present. This stage varies widely in incidence and intensity. It may not appear at all or may last up to several weeks.[59]
- A stage in which behavior is organized rather than random, and the patient is responsive to questions. There may be features of both the amnestic confabulatory state and the syndromes of denial, with anterograde and retrograde amnesia, confabulation, environmental and temporal disorientation, reduplicative misidentifications and delusions, and mood changes. Components vary in duration but may last for weeks and months and the patient later may be amnesic for much of the period. While there are deficits in memory and other forms of cognition, and in attention and perception, the behavior also has positive, symbolic, and adaptive aspects.

Post-Traumatic Amnesia

Anterograde amnesia (AA) is the period of time following the traumatic event or interruption of consciousness during which the patient is unable to retain new information and for which he later has no recall. Retrograde amnesia (RA) is the span of time prior to the injury that the patient does not recall. While post-traumatic amnesia (PTA) usually

has anterograde and retrograde components, these may be dissociated and may have different mechanisms.[60,61] The length of the AA is a good indication of the severity of the brain injury but the extent of the RA is much more variable. A study of a group of soldiers with severe head injuries admitted to Walter Reed Army Medical Center showed that while some patients had extensive RA reaching back for years with no recollection of having served in the U.S. Army, others with comparable injuries had RA of days or weeks.[62] It is important to note that the events took place at a time when the patient's brain was functioning normally, while those of the AA occurred while he still had not attained full consciousness. The duration of the AA roughly corresponds to the period of time over which the patient was unconscious, confused, or disoriented. When interviewed later, patients are apt to estimate the length of the AA in terms of when they "woke up."

It may be difficult to precisely determine the duration of an RA from the patient's verbal report. For example, a patient may state that he remembers nothing since embarking on a trip days or weeks prior to his injury. On further questioning it turns out that he does not know the destination or purpose of the trip, even though it had long been planned. Some patients have a temporal gradient in accordance with Ribot's law, which states that memories more remote in time are spared. There are, however, many patients who do not show a temporal gradient.[61,63]

AA and RA differ in respects other than their temporal relationship to the traumatic event. Patients are likely to be unaware of an RA but may complain about their inability to retain information. The time span of the AA tends to remain fixed in terms of later recall, while the RA, on the other hand, shrinks in the course of clinical recovery so that eventually it covers only the seconds, minutes, or hours immediately preceding the traumatic event or loss of consciousness. While the moments preceding the loss of consciousness are irretrievable, earlier events may sometimes be recovered under hypnosis.[64] Interestingly, functional amnesias and fugue states not associated with brain damage are wholly retrograde.

RA involves more than memory loss per se in that it may be associated with feelings of unreality. Patients may not believe that they were actually in an accident, despite having been told about it many times, and despite the evidence of a cast on a leg or side rails on the bed. Some patients demand to see a photograph of the wrecked car, and even then may claim it is a different car. A soldier wounded in combat in Korea refused a Purple Heart, stating that if he had been wounded he would know it. Even after patients acknowledge that they have been injured, they may preface their answers to questions of what happened with "I don't know," "I don't remember," and "They say that..." There may be *jamais vu* experiences. A soldier returning home on leave said that he felt he had never been there before. Another complained that the old songs he knew were not familiar anymore.

Amnesic patients may have implicit knowledge of events that they cannot consciously recall. Performance may improve with successive trials on tasks that the patient may not recall having done previously. Soldiers who could not remember having been in the service retained knowledge of military protocol, and men who could not remember having been married could still recognize their wives. In one such case the patient commented that he knew his wife from their courtship days.

Amnesia can have positive as well as negative aspects in that the patient's last memory prior to "waking up" or "coming to himself" in the hospital may be a symbolic representation of current experiences and problems. Thus, the last memory of a patient with severe visual loss was of getting a new lens for his camera a few months before his injury. Such last memories may be veridical, actual events displaced in space and time, or confabulations. As new problems develop in the course of recovery, so may new last memories appear. A characteristic "last memory" occurs in patients who have been in an accident that resulted in fatalities. This has to do with sleep or other loss of consciousness; going to bed the night before, napping in the back seat of the car, or passing out at drill a few days previously. Over the period in which such memories are recalled, the patient usually expresses no conscious awareness that someone has been killed.[65]

Anosognosia

Anosognosia—literally lack of knowledge of disease—is closely related to amnesia as patients deny that they were injured or were in an accident. They may also disclaim such disabilities as hemiplegia, blindness, paraplegia, loss of a limb, facial disfigurement, and a craniotomy or tracheostomy. Patients may flatly deny that they are disabled in any way, or minimize impairment by attributing a paretic limb to a sprained ankle or "laziness." Some acknowledge the disability but regard it as outside of the self, referring to it as an animate or inanimate

object or in the third syntactical person as "he," "she," or "it." They may claim that the accident happened to another person and do not get upset when their erroneous statements are challenged. Some claim that their disability was caused by rough handling by the hospital staff.[66] Many anosognosic patients, like amnesics, may appear quite normal on casual examination. Denial may also be expressed in the form of joking and punning and caricaturing disabilities.

As in amnesia, patients may indicate implicit knowledge of their problems and traumatic experiences, as in the case of a woman who denied that she had had a craniotomy but who complained of the "sawing and hammering" on her head. Selectiveness is another indication of awareness at a less-than-conscious level. Patients are not delusional or confabulatory about a part of the body that is not disabled in some fashion. Denial of physical disabilities usually clears within weeks, but denial of memory loss and other cognitive impairments may endure for months and years.

Laterality plays little role in the amnestic confabulatory state, which appears most prominently after bilateral orbitofrontal, anterior temporal, paralimbic, and diencephalic damage. Anosognosia occurs more frequently after right hemisphere lesions than after those of the left hemisphere. Such pathology is usually extensive and involves more than one lobe. In anosognosia for hemiplegia there is usually both frontal and parietal lobe damage. Patients with left hemisphere pathology may deny their aphasia, which is usually of a fluent type, often with jargon. Denial of memory loss is a feature of frontal and diencephalic amnesias in which the brain damage is bilateral.

Confabulation

Confabulations are defined as fictitious narratives without intent to deceive, or distorted versions of actual events. Some are spontaneous, fantastic, and unrelated to the person's experience, but most confabulations after brain injury are elicited in response to questions about the patient's disability and reason for coming to the hospital. A study of 100 moderately and severely head-injured patients seen at Walter Reed Army Medical Center found that 60 confabulated at some time during their hospital stay.[67] Initially confabulations tend to be brief, multiple, contradictory, and transient, but, after the stage of agitation, a patient may maintain a confabulation for weeks and months. Some, particularly early ones, are confabulations of exigency, as in the instance of a patient with his arms restrained who claimed that he had been shot in the hands. Others are amplifications of denial, as in the case of the man who explained his hemiparesis by stating he had sprained his ankle in a football game. Other confabulations are not associated with explicit denial, but are dramatizations, or allegorical or metaphorical representations of the patient's problems and disabilities. Although ostensibly referring to *past* events, they may symbolize the patient's *current* situation. The following is illustrative.

Case Study 1: Confabulation Following TBI

A 42-year-old field-grade supply officer sustained a head injury in Korea when his jeep overturned. He was left with slight weakness of his right upper extremity, and mild dysphasia, dyslexia, and dysgraphia. He was seen at Walter Reed Army Medical Center 4 months after his accident. When asked what had happened to him, he gave the following story, to be repeated on many occasions:

> I had a big job overseas. I was an intelligence officer for the Air Force. The man I replaced was a captain and his assistant a first lieutenant so that the two of them were working with me. I was sent to check on their security. They were just as Commie as if painted with a red brush. I had to write out everything I found so that it could be read in court in a court-martial for these men some day. I wrote it out and turned it into headquarters. I had enough written so that any jury in the right senses would give these guys 40 years in jail right away; they were just that Commie….[68(pp386–387)]

Comment: The repeated reference to reading, writing, and right senses and to intelligence indicate the patient's knowledge of his impairments, not otherwise expressed. The case also helps explain why patients may include apparently circumstantial and irrelevant details in their narratives and repeat them in each telling.

A new confabulation or a change in the content of an old one may indicate a new stressful experience. In the case just described, the patient was refused permission to visit his wife. He appeared angry but said nothing, but the next day he included a detail about threatening to shoot a man for giving food to Communists.

The content of confabulations is determined by several factors. One is the nature of the stress or disability. A second involves popular topics in the news such as Communism and space travel. A third factor concerns those themes that in the patient's past experience have been significant elements in patterns of social relatedness and important sources of identity. The Walter Reed study[67] showed that more than one half of the confabulators referred to

family members, real or fictitious. They stated that a brother, child, or parent had been in the accident, often sustaining an injury identical with the patient's own. Confabulations about work and occupation were less frequent but were longer and more elaborate. Paratroopers injured in car accidents or fights were apt to confabulate that they had been hurt jumping and the inclusion of expressions like "had a Mae West" lent verisimilitude to the story. Confabulations about sports and minor illnesses were usually associated with denial of disability. Confabulations about great violence and death were associated with more disturbed behavior and somatic symptomatology.

As in amnesia and denial, patients may show implicit knowledge of the disability or traumatic event. This may appear in the content of the confabulation, as in the case of a soldier with a tracheostomy who confabulated that he had been a vocalist in a 17-piece band.[68]

In the course of clinical recovery, the content of an erstwhile confabulation may be represented in other forms of disturbed behavior. Following a head injury sustained in a car accident, a soldier confabulated about a girl passenger whom he said he had saved from injury by shielding her head at the moment of the impact. He was left with a left homonymous hemianopia, and on his first leave home, became extremely worried that a neighbor's child would go blind. He then became engaged to a 15-year-old retarded girl in the hope that U.S. Army doctors could operate and cure her.[67]

Environmental Disorientation

Disorientation for place or environmental disorientation takes on different forms depending on the stage of recovery. During the period of agitation, responses are random; the patient places himself at work, in combat, in a bar. As his behavior improves, disorientation may appear in successive patterns of misnaming, mislocation, condensation of time and distance, and the confabulated journey.[69,70] Patients usually say that they are in a hospital but they give it the name of another hospital, real or fictitious, or use euphemisms like "place for R and R," "repair shop," "retreat." In misnaming, the patient most often selects a hospital situated at his training base or in his home town. The patient may then name the hospital correctly but mislocate it in places associated with work or home. Or, a soldier may go on to name and locate the hospital accurately, but greatly condense the distance or travel time between the hospital and his home or base. After a patient appears to have established complete orientation, he may offer a confabulated journey as in the case of a soldier who stated that he had flown to Florida that morning.

Patients maintain their disorientation despite cues, clues, and corrections. Even with the name of the hospital in full view on bed linen, staff name tags, and desk plaques, and, despite having been told, patients refuse to accept the proper designation. The following case is illustrative.

Case Study 2: Environmental Disorientation Following TBI

A 21-year-old soldier was admitted to Walter Reed Army Medical Center after having sustained a head injury and a traumatic amputation of his left arm in an automobile accident. His home was in Massachusetts and he had been traveling to Washington from his station in Georgia. He denied that he had lost an arm and stated that he was in "Coolidge Memorial Hospital," which he located in Georgia. (It was later learned that the name was a condensation of Cooley-Dickerson Hospital and the Coolidge Memorial Bridge near his home.) Over the next 2 months, he successively located "Coolidge Memorial" in North Carolina, Virginia, and Washington. Then it became "Walter Reed Memorial Hospital." He gave up the disorientation with apparent reluctance, "they say it's Walter Reed or something," "it's supposed to be Walter Reed." At the same time he admitted the loss of his arm. Throughout the remainder of his 5-month hospital stay he was oriented, but expressed a "feeling that there must be a Coolidge Memorial Hospital somewhere."[66(pp46–47)]

Comment: Enduring environmental disorientation is not explicable in terms of confusion or overall memory loss, but has positive motivational aspects. Here the patient clung to his delusion in an apparent effort to maintain identity.

Temporal Disorientation

Disorientation for date and time of day are associated with environmental disorientation and RA. Patients displace backward in time and the greatest displacements occur in patients with amnesia of long duration.[71] In disorientation for time of day, the patient confuses morning and afternoon, and AM and PM. He appears to gauge the time in terms of his personal experiences and activities. No matter at what time of day he was examined, one man usually said it was 3 PM because that was when his wife visited. Disorientation for time is particularly striking after a patient has been sleeping or dozing. A man served with supper after awakening from an afternoon nap was indignant over having been given "spaghetti for breakfast." Such temporal disorientation occurs even with a large wall clock in full

view, and when the patient is permitted to look at his watch. Nevertheless, such patients may be quite capable of drawing a clock and putting the hands at a designated time. Similarly, in disorientation for date, a patient may persist in his misdesignation even after being told or shown the correct date. Disorientation for person will be considered under the reduplicative disorders.

Reduplication

Reduplicative delusions and misidentifications occur in a number of modalities; those of place and person, time and event, objects, parts of the body, and the self. One form is usually associated with another. Like anosognosia and environmental disorientation, right hemisphere lesions are more common than those on the left even though both sides of the brain are usually involved.

Environmental reduplication or reduplication of place is the belief that there are two or more places of the same name although only one actually exists. The first case, in a woman with senile dementia, was described by Arnold Pick in 1903 under the designation, reduplicative paramnesia.[72] Henry Head[73] reported the case of a British soldier in World War I who, after sustaining a frontal missile wound, thought that there were two towns of Boulogne in France—one that he traversed on his way to the front, and the other through which he passed on his way home to England on leave. Head remarked that the man appeared rational in all other respects except that he wrote letters to his mother even though he knew that she had been dead for years.

Reduplication of person is the belief that a person has more than one identity. A soldier may believe that a corpsman is also a cook in his unit. In the syndrome of Capgras, which is not infrequent after head injuries,[74–77] the patient believes that a familiar person, usually a close relative, is an impostor. Another form of personal reduplication is the belief that one has an "extra" child.

Temporal reduplication is the belief that a current event has also occurred in the past, an enduring déjà vu experience. Patients hospitalized for a car accident state that they have been in several recent automobile accidents, or that they have previously been treated at the hospital for the same condition. It may be difficult to separate temporal from personal reduplication, as in an instance in which a patient claimed that a nurse was a high school classmate.

Patients may reduplicate both inanimate and animate objects, as in claims that personal possessions and domestic pets have been replaced by facsimiles. In reduplication of parts of the body, a patient believes that he has more than two arms, two legs, or one head. Reduplication of the self involves the belief that one's self is elsewhere or that one has a double.

The incidence of reduplicative phenomena in head injury varies with the method of study. Patients may not offer their beliefs unless specifically asked, and some do not volunteer them because they recognize their unusual nature. In the Walter Reed study[67] reduplication was found in 85% of patients, excluding those who were markedly aphasic or severely withdrawn. Reduplication is commonly associated with retrograde amnesia, confabulation, denial, and environmental and temporal disorientation, or it may first be noted after these conditions have improved or cleared. In one case a patient originally mislocated Walter Reed in Texas, his home state, then claimed that there were two Walter Reed hospitals, one in Texas, and one in Washington. Feelings of unreality and depersonalization often precede and are associated with reduplication. As noted, patients may not believe that they were really injured, or that people are who they say they are. In some instances, reduplication does not appear until weeks, months, and even years after the injury.

The two or more places, persons, events, objects, and parts of the body, although alike in many respects, are not identical. They differ in some way germane to the patient's experiences, feelings, and problems. For example, a patient admitted for multiple injuries thought that there were three Walter Reed Hospitals, one for head injuries, one for fractures, and one for plastic surgery. Aggrieved patients may believe that the nurses in the "other" hospital were kinder and more considerate. A patient with a draining suboccipital craniotomy wound complained of "bad drainage" from one of his heads, but claimed that his "other" heads were functioning well.[66] Alexander, Stuss, and Benson[75] studied a man who for several years after his head injury claimed that his family had been replaced by another almost identical one. The only difference was that the children of the "first" family were about a year younger than those of the "second" family. This difference appears to correspond with the period over which the patient estimated he had been disabled. The authors noted that the patient recognized the implausibility of his story while maintaining its correctness. He behaved in his usual manner toward his wife, showing neither anger nor distress at her putative desertion. With the break-

down in the unities of time and space, the "extra" person becomes a condensed symbolic representation, a reification or personification of the patient's own experience.

The delayed onset of reduplication and its relationship to depersonalization and derealization is well shown in a case reported by Staton, Brumback, and Wilson.[76] The patient had had a car accident at the age of 23 followed by a week of coma. He made what was apparently a good immediate recovery but several months later had episodes of irritability and complaints of memory difficulties. In the first few months after his accident he experienced feelings of unreality but did not report them until 4 years later. At that time he expressed the conviction that all of his current experiences had happened before. When examined by Staton et al 8 years after his accident, he described living in a world of fantasy in which his relatives were not the people he had known but were slightly different "look-alikes" or "doubles." The family farm was a false duplication because recent buildings looked like they should not have been built. Even his cat was not real because of a scar on its ear. He denied that he could be his real self because he was missing a tooth and wasn't working. He believed that the entire 8-year period of disability and unreality lived since the accident had occurred at some time in the past and resulted in complete recovery.

Reduplication and accompanying phenomena are adaptive in that patients expressing them are often less agitated and disturbed than they had been previously. Reduplication and confabulation combat feelings of unreality and nothingness, and the reification of an experience in terms of a place, person, or event may make it more "real" in the sense that metaphor may make reality more vivid. The validity of the denial and other symbolic representations of the patient's problem is reinforced by the way the content of the delusion identifies him with such significant values as home, family, work, health, and survival. Moreover, the delusion brings certainty, order, and unity to what would otherwise be masses of disparate, confusing, and contradictory data.

Mood Disorders

In general, the most conspicuous mood changes occur in patients in whom there is a relative paucity of verbal adaptive mechanisms. Patients with explicit denial tend to be bland and unconcerned, sometimes euphoric and witty. Those with partial denial might admit problems but attribute them to the inefficiency or malice of the staff. Patients without denial may be withdrawn and depressed, making references to being in a prison camp or cemetery, and such behavior may be punctuated by episodes of agitation. Others are hypomanic and ludic—a term introduced by Jean Piaget to describe the play and imitative aspects of the behavior of young children. These patients clown and joke, and caricature their disabilities. In their melodramatic presentations comic and tragic aspects are intermingled.[78] Altered sexual behavior is not uncommon, with lewd remarks, verbal and physical advances to staff, and confabulations of sexual activity. Aggressive and violent behavior may appear, often as a withdrawal manifestation, analogous to alcohol withdrawal, in patients who recover full consciousness rapidly and must face a new environment without going through a stage of denial and other adaptive coping mechanisms. As in anosognosia and reduplications, lesions are more likely to involve the right than the left hemisphere.

NEUROPSYCHOLOGICAL ASSESSMENT

Neuropsychological testing covers the areas of attention, memory, language, calculation, constructional and visuospatial skills, praxis, abstraction, and executive functions. It should be borne in mind that these categories are, in some degree, abstractions in the mind of the examiner rather than models of the organization of the brain. A single test may tap a number of functions. Clock drawing with the placing of the hands to a designated time, for example, requires attention, visuospatial, and constructional skills, and the ability to recognize that a 5 in one context means 25 minutes after the hour, and that in another it indicates the hour itself.

Formal neuropsychological testing is not performed during the first few weeks postinjury, because of impairments in attention, concentration, and inhibition, and because changes in the perception of reality do not lend themselves readily to tests for neural deficits. There are, however, a number of measures that can be used with the disoriented patient. The Galveston Orientation and Amnesia Test (GOAT) documents the disorientation, and estimates the duration and severity of the

PTA.[79] Patients are asked for the last event they remember before the injury, and for the first thing they can remember after it. Other tests that make minimal demands on the patient are tasks of reaction time, object naming, verbal fluency, and letter cancellation. The patient's ability to spell the word WORLD forward and backward and state how many nickels there are in a dollar and how many dollars there are in 60 nickels is a valuable index of cortical function. These measures can aid the investigator in establishing the recovery slope and determining when more extensive neuropsychological testing can be accomplished.

Attention

Two types of attention are recognized. A tonic form refers to the level of vigilance regulating overall information processing capacity. The second is a vector function, which regulates the direction and target of attention in any one behaviorally relevant area or space. Tonic attention is related to the activity of the reticular activating system. Directed, selective attention is associated more with neocortical activity. Marked disturbances of tonic attention are found in the acute confusional states in which the patient is highly distractible and cannot maintain vigilance, is unable to pursue coherent thought, and is unable to carry out a sequence of goal-directed movements. Impairment of focal directed attention is found in hemineglect in which a patient ignores or is unaware of one side of his body, or one half of circumambient space, or both. It occurs mainly with right hemisphere lesions involving the parietal and frontal multimodal association areas and their limbic, reticular, and sensorimotor connections.[80,81]

Overall attention can be tested by measuring digit span. The examiner orally presents a string of digits to the patient at a rate of one per second, and asks him to repeat the list forward and then backward. A normal digit span forward is five to seven items, and in reverse it is two digits less.[81,82] Sustained concentration can be evaluated by the "A" test in which the examiner reads aloud a list of 60 letters at a rate of one per second and the patient signs by raising his hand when he hears the letter "A." Normal persons perform error free while patients with deficits in attention tend to make errors of omission. The tendency of patients with impaired attention to have difficulty in inhibiting responses can be evaluated with a "go-no-go" paradigm. The patient is asked to raise his index finger when he hears a single tap and to make no response to two taps, which the examiner makes by hitting the undersurface of the table out of the patient's vision. In the Stroop interference procedure the patient is presented with color words, each printed in a color other than that spelled by the letters. The task is to give only the color and to inhibit the tendency to read the literal spelling.

Hemineglect has perceptual, motor, and motivational components. In drawing a clock the patient may omit the numbers on one side or in representing a daisy he may similarly leave off the petals on one side. Drawing of a human figure may show only one arm, leg, eye, and ear. The patient reads the word BRAKE as RAKE, or in the instance of right-sided hemineglect reads HERON as HERO. Writing may be confined to one side of a page. If the patient is asked to bisect a horizontal line he is likely to draw the vertical line on the side of the midline ipsilateral to the lesion. When both sides of the body are touched simultaneously the patient reports only the stimulus on the intact side, although a single stimulus on the affected side can be perceived, a phenomenon known as extinction. If the patient is asked to raise both arms aloft he may lift only one extremity, even though the other one is not weak and he uses it in other activities. On a letter cancellation task, performance in the detection of targets on the involved side may be improved by offering a reward.

Memory

There are various types and classifications of memory and memory loss. These include the amnesias; immediate, short-term and long-term memory; recent and remote memory; verbal and nonverbal memory; modality specific (visual, auditory, olfactory), episodic (autobiographical, specific events in time and space), semantic, and procedural (facts, procedures, skills) memory; and memory for geographical places, for people, and for animals. Testing therefore can be highly specialized.

Because of such specialization amnesics may do well on many recall tests, especially if they are allowed to rehearse silently. Rehearsal can be prevented by the Brown-Peterson interference technique, based on the known sensitivity of patients with AA to distraction. The patient is presented with trigrams or groups of 3 words over varying intervals, and asked to count backward aloud during the intervals. Performance is far inferior to that which would be accomplished had rehearsal been permitted. The Famous Faces test in RA is based on

the concept of a temporal gradient. The patient is asked to recognize the faces of people prominent in the news over periods in the past, and scores for different decades compared. However, because autobiographical memory can be profoundly impaired while knowledge of famous people and events is spared[83] and a considerable number of patients do not manifest temporal gradients, the test is of limited clinical value.

Story recall is routinely used. The patient is asked to recall a 6-item passage such as "St Joseph's School burned down and 3 firemen were overcome by smoke" immediately and after an interval of 5 minutes. Nonverbal memory can be evaluated by having the patient watch the examiner conceal several of his personal possessions, and find them 5 to 10 minutes later. A more complex evaluation of verbal memory can be done through the Rey Auditory Verbal Learning Test. The Rey-Osterrieth Figure Test provides a quantitative measure of nonverbal learning and memory.[84]

Language

Evaluation of language functions mainly concerns aphasia. Patients are tested from the standpoints of fluency of conversational speech, comprehension, repetition, reading and writing, object naming, and word-word relationships. Note should also be taken of handedness.

Nonfluent aphasia is characterized by sparse verbal output (less than 50 words/min), effortful speech, short phrase length, sometimes a single word, poor articulation of speech sounds, and dysprosody, the loss of melodic quality.[85] Agrammatism, the omitting of function words such as "and" and "to," and of syntactic indicators such as verb tenses and plurals, may be a feature. Fluent aphasia, on the other hand, involves a normal or excessive production of words, normal phrase length, and intact articulation and prosody. There may be paraphasic word errors, and jargon, the use of neologisms or standard English words given in meaningless or inappropriate contexts. Nonfluent aphasias occur with lesions of the anterior dominant, usually the left, hemisphere while fluent aphasias are found with more posterior lesions.

Comprehension is tested by having the patient follow commands: Point to the window, Clap and clasp hands, Stand up and walk to the door. If severely impaired or apraxic he can be asked questions such as, "How many wheels are there on a bicycle?" or asked to give yes or no answers to questions such as, "Are the lights on in this room?" or "Did George Washington have a beard?" The patient may be asked to decipher passive sentence structures such as "The lion was killed by the tiger; which animal is dead?" Comprehension can be impaired by lesions of both anterior and posterior parts of the left hemisphere.

Repetition can be tested by having the patient repeat words, phrases, and sentences. Aphasic patients generally have more difficulty in repeating passages with function words such as "no ifs, ands, or buts" than they do with phrases containing content words such as "correspondents write frequently." Failure of repetition is a cardinal feature of conduction aphasia produced by lesions of the perisylvian area.

Reading should be assessed both by reading aloud and testing comprehension. While alexia without agraphia is a reliable sign of a posterior left hemisphere lesion, alexia and agraphia may occur with lesions at various points in the hemisphere.

Writing can be evaluated by asking the patient to write his name, and take down a dictated sentence. Note is made of word accuracy, spelling, and calligraphy. Disorders of writing are common in confusional states and are of limited value in localization.

The patient is asked to name common objects and movements or pictures of them, along with colors. Items that are most apt to yield errors are those that are parts of wholes, such as a button hole, cuff, or lapel, or have compound names such as doorknob or coathanger. Color anomia may occur in association with alexia without agraphia. Generally, aphasic naming errors are not of value in localization. Nonaphasic naming errors may also occur with lesions of the right hemisphere and with bilateral damage. These are apt to involve items connected with the patient's disability or that have other personal significance for him, as in referring to a wheelchair as "a director's chair" or a plastic drinking straw as a "cigarette."[86]

Calculation

In testing a patient's ability to add, subtract, multiply, and divide it must first be determined that he can comprehend the concept of an arithmetical operation, and that he is attentive to the task. Serial subtractions of 7s is a useful test that depends not only on calculation skills but on attention. Normal persons may make errors in the unit column, so that the significant mistakes are in the tens column such as "93, 76 …" or "93, 86, 79, 82." Tests of addition and subtraction should involve carrying, and in evaluating multiplication, rote tables should

be avoided. The finding of dyscalculia is not of great localizing value but the combination with agraphia, difficulty in identifying and naming fingers, and left right disorientation is highly suggestive of a lesion in the left parietal lobe.

Constructional and Visuospatial Skills

These are tested by drawing and making designs. The patient is asked to draw a clock, house, or cube, or copy a complex design like the Rey-Osterrieth Figure. In the block design subtest of the Wechsler Adult Intelligence Scale, the patient arranges a group of colored blocks in a design shown on a card. Impairment occurs with lesions of either hemisphere. Evidence of hemineglect may also be found in the drawings of patients with right hemisphere lesions. Topographical orientation and memory can be tested by having the patient draw a map of his quarters or describe a familiar route. Impairment occurs with both bilateral and unilateral posterior brain lesions, the latter located more frequently in the right hemisphere.

Praxis

Apraxia is the inability to carry out a skilled movement on command or in imitation even though the person understands the task and there is no primary motor disability. Ideomotor apraxia is the inability to perform an act, such as a salute, although the patient can do it spontaneously. Ideational apraxia refers to the failure to carry out a sequence of actions, such as folding a letter, putting it in an envelope, and sealing it. The ability to pantomime may also be tested by asking the patient to pretend to comb his hair, brush his teeth, cut with scissors, and fire a pistol. An apraxic patient is apt to substitute a body part for the object. He may run his fingers through his hair, rub his index finger against his teeth, use his index and middle fingers as scissor blades, and point his index finger and say "boom, boom." Serial hand movements can be tested by having the patient assume three consecutive hand postures, first in a fist position with the knuckle downward, then with hand open and palm down, and then with hand open and edge down while saying the positions aloud, "fist, slap, cut." Ideomotor apraxia is often associated with aphasia, but other forms are difficult to localize. Interestingly, apraxic patients rarely complain of any difficulty.

Dressing apraxia is the failure of a person to put on a coat or a pair of trousers after the garments are handed to him. He may get the sleeves reversed or even try to put both legs into the same trouser. It is considered to be a constructional difficulty rather than a true apraxia. It may occur with right parietal lesions along with topographical disorientation and hemineglect, and is common in dementia and confusional states.

Abstraction

Abstraction is the derivation of a common principle or category from diverse elements. In the Similarities subtest of the Wechsler Adult Intelligence Scale, the patient is asked how such items as a chair and a table, or a cup and a saucer are alike. Aphasic difficulties and loss of inhibition may contribute to failures as in the statement that "You drink from a cup." Proverb interpretation is commonly used, but has the disadvantage that most proverbs are overlearned and do not require abstract thinking. Nonverbal categories can be tested by asking the patient to sort out stimuli on the basis of color, shape, or size. Impaired abstraction is traditionally associated with frontal lobe lesions, but may be a feature of more widespread brain involvement.

Executive Functions

Defects in executive functions are characterized by inability to plan and organize behavior and set priorities among competing tasks. Such a patient may do well on a large battery of neuropsychological tests including those of memory, abstraction, and reasoning.[87–89] He might answer a test question of what he would do if he found a stamped and addressed envelope on the street, but act quite differently. Testing should approximate real life situations. Loss of executive functions with preservation of other faculties is a reliable indicator of focal frontal lobe damage.

LONG-TERM SEQUELAE

The long-term sequelae of TBI cover a broad range of cognitive, affective, and personality changes. While some patients show striking changes in language, perception, and visuospatial processing, the more typical picture emphasizes disturbances in memory, attention, personality,

and the cognitive and affective aspects of social behavior.

Cognitive Changes

Memory problems include a deficit in the explicit retrieval of new information (AA), and a much more modest and variable RA. Immediate recall and older memories are generally intact as are implicit memory processes. The deficit thus appears to be primarily in the consolidation of new episodic memory. These memory problems may be accompanied by slowed reaction times and reduced information processing skills, attentional deficits, and impaired ability to divide cognitive resources. Related to this may be a deficit in concept formation with difficulty in changing set, manifested by perseveration on such tasks as the Wisconsin Card Sort Test.

The follow-up study of head-injured Vietnam veterans showed that damage to the basal forebrain (BFB) in the proximal orbitofrontal lobe made a large contribution to the episodic memory loss as well as to the slowed reaction time and attentional deficits. BFB-injured men differed from their non-BFB-injured matches only in having a longer loss of consciousness postinjury, more episodic memory deficits and poorer performance in the Wisconsin Card Sort Test.[90,91] The basal forebrain lesions alone, however, were not sufficient to produce dementia as suggested by studies of Alzheimer's disease.

In addition to residuals of aphasia, there are nonaphasic disturbances of language that are more difficult to classify. These include tangential and fragmented speech, loose connections between words and ideas, cryptic expressions, and a tendency for the patient to refer to himself and his experiences in the third person. Thus, he may describe his injuries as if they had happened to someone else.[62,92,93] These nonaphasic language disorders are mentioned not because they appear in a majority of patients but because they may be mistaken for schizophrenic phenomena.

Affective Disorders

These depend only partly on the severity of the brain injury and the location of the lesion. The disorders are also influenced by associated verbal behavior, premorbid experience, and by environmental events. Efforts to localize individual mood states have led to variable, sometimes contradictory, results.

Anxiety

Anxiety has traditionally been regarded as a reflection of the patient's efforts to cope with his deficits and the social limitations imposed by them. Extreme degrees of anxiety are expressed in the catastrophic reaction, a term introduced by Kurt Goldstein[94] to describe the behavior of brain-injured German veterans of World War I. It consisted of outbursts of frustration and emotional distress experienced by the patient confronted by a task or situation beyond his capabilities. Catastrophic reactions occur predominantly in patients with left hemisphere lesions, especially those situated anteriorly, and associated with nonfluent aphasia. A study of Vietnam veterans seen 15 years after injury showed, however, that feelings of anxiety and "edginess" were experienced most frequently by men with right orbitofrontal damage, while feelings of anger/hostility were most frequent after left dorsofrontal lesions. Generally, patients with orbitofrontal lesions appeared more affectively blunted and hostile than any other lesion group or controls.[2] The study also showed that cognitive deficits played a lesser role in right hemisphere mood change than they did in left hemisphere lesions.

Some forms of anxiety disorder have been related to serotonin excess[95] or excessive neuroadrenergic activity.[96] Other neurotransmitter systems including γ-aminobutyric acid (GABA) have also been implicated in anxiety disorders.[96]

Denial or Unawareness

While anosognosia for physical defects such as hemiplegia usually clears within 2 or 3 months, denial or unawareness of cognitive and other behavioral disabilities may persist much longer. The so-called anosognosic attitude, while it combats anxiety and depression, may lead to a number of undesirable consequences. The patient may blame his problems in social relationships on weakness or an unsteady gait. He may have unrealistic work expectations, and be unwilling to accept a job that he feels is beneath his capabilities. He may see no need for training or rehabilitation.

In the early stages when the anosognosia is complete and has the supporting cognitive framework of confabulations and delusions, the patient is usually serene, but as brain function improves, he may become anxious and depressed. He may develop headaches and other somatic complaints. He may become obsessively concerned with his own health and that of others. He may express concern about

minor facial blemishes or his teeth, and express fears of falling or getting a haircut. Some patients become preoccupied with God and sin and leading a better life. Paradoxically, the patient becomes more emotionally disturbed at a time when his brain function is recovering.

Dealing with denial and the catastrophic reaction is a major task of neuropsychological rehabilitation, and unless these phenomena are dealt with, improvement in psychosocial adjustment is much less likely to occur.[93] Awareness allows the patient to experience a normal grief reaction and adjust to lost skills and loss of status. On the other hand, other patients with severe brain injuries remain aware of their problems. A soldier who had returned to duty complained on follow-up that it was difficult for him to make new friends because he could not stop himself from talking so much.

Depression

Depression in the form of feelings of helplessness, unworthiness, guilt, reduced self-esteem, loss of interest and initiative, and diminished libido is a common later sequel and can appear at any time postinjury. Depression is not directly related to the severity of the brain injury or the degree of neuropsychological impairment.[93,97] The depression may not be a classical one, worse in the morning, and associated with weight loss and psychomotor agitation or retardation;[98] however, the classical symptom of insomnia is common. Social withdrawal may be a feature of depression, but in other instances it may be simply the avoidance of coping with a stressful situation.[93] Decreased sexual drive and diminished erectile function may or may not be associated with depression.[99] While reduced sexual drive along with cognitive loss, and physical complaints like headache and fatigue are factors in troubled domestic relationships, increased sexual drive may also be a problem.

Location of the lesion is another determinant. Major depressions are more common after left than right hemisphere lesions, with the greatest frequency following left frontal damage.[100,101] Depression, however, is also common with right hemisphere pathology, especially in patients without denial and the associated phenomena that have been described.[93,102] The hemispheric asymmetry has been attributed to differences in cognitive capacities of the hemispheres, to the adaptive role of denial, confabulation, and reduplication, and to direct biochemical effects. Some forms of depression appear to be related to depletion of brain serotonin,[103] and it has been shown that after brain injury there is increased serotonin receptor binding in intact areas of the right hemisphere suggesting better biological adaptation.[104]

Premorbid experience and the quality of psychosocial functioning also play a role in depression following brain injury, and in later-onset depression these factors are of greater importance than lesion location.[105] A recent civilian study of acute and late-onset depression after closed-head injuries found that patients in both groups had more psychiatric disorders and poorer social functioning than controls; but, while acute onset depression was significantly related to left anterior frontal lobe localization, late onset depression was not related to the site of brain damage.[105]

Secondary mania after TBI is far less common than depression as a long-term sequelae. Case reports indicate onsets of from weeks to years postinjury with involvement of orbitofrontal and basal temporal regions and other subcortical structures, and greater on the right side of the brain.[106–108]

Aggressive and Paranoid Behavior

Aggressive behavior may appear at any time after a brain injury. Outbursts of temper with verbal and physical aggression may be a response to frustration, and be triggered by small amounts of alcohol or other drugs. Violence in the sense of directed physical force against persons or property may occur when the patient feels that he is being threatened or persecuted or will be harmed, and also in the absence of paranoid delusions. Paranoid attitudes may be expressed in justification of acts of violence. When episodes of explosive rage are out of proportion to any precipitating stimulus and especially when they are followed by amnesia, they raise the question of temporal lobe epilepsy. It is likely, however, that the incidence of both posttraumatic temporal lobe epilepsy and directed assaultive destructive behavior in epilepsy has been exaggerated.[109–112] More relevant considerations are a history of severe combat stress, violence in civilian life, and the immediate environmental situation. While a history of head injury is very common among patients who come to medical attention because of violence, the incidence of violence in controlled follow-up studies of patients with head injuries is far lower. A 5-year follow-up study of 1,830 Finnish veterans of World War II, 32 to 37 years after the end of the war, who had sustained pen-

etrating brain injuries did not show a higher frequency of violent crime than did nonwounded veterans. Nor was there more violent crime in men with frontal or temporal lobe lesions.[113]

The Overt Aggression Scale[114] grades a spectrum of aggressive and violent behavior ranging from verbal threats, curses, and insults to physically destructive acts against objects, to physical harm to the self, to physical aggression against other persons.

Psychoses

Psychosis can be a late sequel of combat-incurred brain injury recognized months, years, or decades after the trauma. A review of the German literature of the Franco-Prussian War of 1870 to 1871 by Adolf Meyer[115] noted that less than 1% of soldiers with serious brain damage became insane, but the belief that dementia praecox, catatonic psychoses, and schizophrenia could be caused by brain trauma was prevalent during and following World War I. Long-term follow-ups of American casualties of World War II are not available, but a Soviet investigation of 1,168 brain injured veterans reported a 9.8% incidence of schizophrenia mainly of the depressive-paranoid and depressive types.[116] It can be pointed out that many diagnoses of schizophrenia were made before standard classifications were established and before the delusional misidentification reduplicative syndromes of organic origin and the metabolic dementias were well known.

More recent studies, notably those of Finnish veterans of the 1939 to 1944 wars with the Soviet Union, have shown that brain trauma is not a significant cause of schizophrenia. In the Finnish series, schizophrenic psychoses appeared more frequently in men who had had mild head injuries and had not lost consciousness than in the more severely injured, and there was a larger proportion of patients under the age of 20 at the time of the wounding than there was in the 20- to 34-year-old group.[117] A British study[118] found that while the number of schizophrenic-like states following brain damage exceeded that expected by chance, schizophreniform reactions were more frequent than process schizophrenia, and there was no increase in genetic loading.

The most extensive and detailed investigations of psychoses following combat-incurred brain injuries have been carried out at the Kauniala Hospital for Disabled War Veterans in Finland where the treatment and rehabilitation of all brain injuries from World War II are centralized. Investigators there have found a rising incidence of psychoses over the past 40 years; rates of 4.4% in 1951, 8.9% in 1969, and 12% in 1993.[117,119,120] A control group of pneumonia patients in the most recent study had an incidence of psychosis of 3.3%. The most frequent diagnoses were paranoid delusional state, major depression, epileptic psychoses consisting of confusional states after seizures, and organic psychosis (dementia). Delusional psychoses lasted less than a year in 28% of cases, and more than 5 years in 40%. Jealousy and the fear of being sexually betrayed constituted the most prominent delusional content.

The delayed onset of psychosis requires explanation. One aspect is that with the passage of time the risk factors for further brain damage, such as the use of alcohol and other drugs including anticonvulsive medication, additional injuries, cerebral vascular impairment, and systemic disease, increase. Second, the damaged brain is more sensitive to the effects of the stresses of living associated with the person's diminished capacities. Another issue concerns the time that a psychotic reaction becomes overt. As in the case reported by Staton et al,[75] feelings of unreality and reduplicative phenomena may long antedate the florid manifestations. Other studies have linked late onset psychoses with epilepsy, even though only a minority of psychotic episodes are associated with seizures.[121]

TREATMENT

One of the most encouraging aspects of TBI rehabilitation is the amazing ability of the young adult brain to compensate for many aspects of injury naturally. Over the past 2 decades, however, it has become apparent that most TBI patients will benefit from some level of TBI-specific rehabilitation. The field of TBI rehabilitation has grown exponentially over this time, but the exact form and intensity of rehabilitation indicated for a given patient remains debatable.

Multiple therapeutic strategies, including coma stimulation, reality orientation, cognitive therapy, speech therapy, occupational therapy, recreation therapy, and music therapy, have been applied to the TBI patient. While selected elements of many of these will undoubtedly prove useful in the

TBI setting, there has been a paucity of scientific validation for these often expensive interventions (including comparison with minimal care, supportive models).

If progress is to be made in this area, rehabilitation modalities must be subject to the same scrutiny for indications, dose, duration of treatment, and efficacy as are other medical treatments, including drugs. The ultimate goal of therapy should be the independence and community reintegration of the patient within his or her limits, rather than the specialized treatment of specific deficits simply because "they are there."

All too often, scarce resources available to the patient are used up in the early acute and postacute phases on evaluation and therapy of deficits that will improve anyway or that are relatively unimportant to the ultimate goal of independence. Some programs may be actually counterproductive by fostering continued dependence. Relatively cost-effective interventions such as training in specific community reintegration skills (eg, decision making) and certain forms of behavioral modification may end up being omitted because the limited funds available were used up in earlier, less relevant therapies.

Although cognitive rehabilitation has yet to fulfill its promise by submission to careful group and case-series analyses, the reality is that most TBI patients will receive some form of cognitive rehabilitation during their postinjury course. In fact, some drug therapies may potentially be most effective when used in conjunction with cognitive remediation programs. Thus, the possibility of rehabilitation-drug interactions when evaluating drug effects on independent variables must be addressed in pharmacological studies by, at a minimum, categorizing the type, frequency, and duration of remediation. More sophisticated studies can adapt both therapy and agent as dependent factors.

Behavioral Management

The treatment of the behavioral consequences of serious brain injuries varies with the stage of clinical recovery. During the initial acute stage of agitation, aiding orientation and cutting down on environmental diversity may be useful. After the initial phase, it should be recognized that denial, amnesia, confabulation, and reduplicative misidentifications are "normal" phenomena and do not have the same ominous significance of delusions in nontraumatic mental illnesses. Barring abnormal neurological signs and impairments from other injuries, patients are usually discharged from the hospital after they become oriented and able to retain new information. They are then reevaluated after a 6-month period over which the greatest part of improvement in cognitive functions occurs.

Caution should be exercised in sending patients with a great deal of denial back to duty or accepting their statements about their condition at face value. Patients about to be discharged from the hospital or allowed leave should be warned about the effects of alcohol, indulgence in which is particularly apt to occur after weeks of confinement. An apparently recovered patient may become disoriented and disturbed after relatively small amounts of alcohol. In anticipating such situations, the Amytal Test described in Chapter 15, Conversion Disorders, is useful. If a patient becomes disoriented or confabulatory under the effects of barbiturates, then alcohol is apt to produce a similar reaction.

While the major recovery of cognitive functions takes place in the first 6 months, patients may continue to make progress in adapting to their deficits. It is doubtful if cognitive retraining is of value in that the damaged brain can relearn lost function, but rehabilitative measures may improve behavior and social skills. The aims of such therapy are to provide the patient with the conceptual or analogical model of what has happened to him, help him to recognize both his defects and remaining strengths, train him in alternate strategies, and teach him how to behave in social situations.[92]

Pharmacological Management

While behavioral rehabilitative measures are the cornerstone of therapy, psychopharmacology has a role in the management of symptoms. Drugs may be indicated for the treatment of depression, agitation, violence, and psychoses, and for the control of pain and seizures. Accounts of anticonvulsant therapy are available in standard neurological texts, and this section focuses on the treatment of disturbances of mood and behavior and of pain in the brain-injured patient.

It must be pointed out that the use of drugs in the control of behavioral changes, particularly agitation and aggression, is controversial and in some situations such control is best achieved by nonpharmacological intervention. Drugs may have undesirable effects, and brain-damaged persons are not only more sensitive to the actions of alcohol and

barbiturates but to those of other drugs as well. Antidepressants, for example, have more sedative, disorienting, hypotensive, and anticholinergic effects than in non-brain-injured patients. Neuroleptics such as the phenothiazines and the butyrophenones may be helpful in diminishing strong emotional outbursts, but they also produce affective and cognitive deficits, lower seizure thresholds, and may actually exacerbate aggressive behavior. These medications may also increase the risk of abnormal involuntary movements and parkinsonism acutely, and tardive dyskinesia, tardive dystonia, and tardive akathisia with chronic use.

In theory, cholinergic, noradrenergic, and dopaminergic drugs tend to activate or increase aggression in TBI patients, while serotonergic (fluoxetine, trazodone) and GABA-ergic (benzodiazepines, valproate) drugs tend to decrease it. In practice, however, pharmacological management of symptoms in a given individual remains largely empirical. The choice of drug is also determined by the postinjury stage. Whereas a neuroleptic like haloperidol may be indicated for acute initial violent behavior, it is contraindicated for later episodes of aggression in a neurologically stable patient.

Pharmacotherapy of Pain

Pain as a direct result of brain tissue damage is uncommon, but headaches are a complaint, and pain may be a feature of associated injuries involving the spinal cord and peripheral nerves. Narcotic analgesics are generally contraindicated in the treatment of chronic pain especially in patients with impaired brain function, and combinations of nonsteroidal antiinflammatory drugs (NSAIDs) and antidepressants are preferred.

Headaches are more apt to be a problem in later stages when patients must face the stress of diminished capability and altered life style. Treatment is much like that of non-brain-injured patients. In headaches of a vascular type ß-adrenergic blockers and antidepressants are often effective. Antidepressants have also been of benefit in headaches caused by muscle contraction. Interestingly, depression rating scales may show little change in the level of depression despite marked improvement in headache control.

Antidepressants probably should be given a different name because they are useful in treating a variety of other conditions including anxiety disorders, panic disorders, PTSD, obsessive-compulsive disorders, bulimia and anorexia, phobic disorders, personality disorders, mitral valve prolapse, peptic ulcers (doxepin is a stronger histamine-2 blocker than cimetidine), and some chronic pain disorders.[122]

The antidepressants of choice for chronic pain appear to be those that affect noradrenergic neurotransmission (imipramine, amitriptyline, desipramine, doxepin, etc.) rather than those affecting serotonergic neurotransmission (fluoxetine, sertraline, fluvoxamine, paroxetine, etc.). An exception to this generalization is fibromyalgia, which appears to respond better to serotonergic drugs. Because the tricyclic antidepressants (including those affecting noradrenergic neurotransmission given above) can lower seizure threshold, patients with head injuries must be carefully assessed. Furthermore, anticonvulsants (most notably carbamazepine and phenytoin) can cause induction of enzymes in the liver that rapidly detoxify tricyclic antidepressants (TCAs), making it difficult to achieve therapeutic blood levels. Some patients respond at dosages of TCAs that would be subtherapeutic for depression; however, many cases require higher dosages. Despite prescribing difficulties, TCAs can give dramatic pain relief.

A report of cases of causalgia resulting from missile and fragment wounds sustained in the fighting in Lebanon from 1975 to 1981 indicated marked relief of pain with phenoxybenzamine, an α-1,2-noradrenergic antagonist.[123] The drug, however, may be contraindicated in head injuries, as it has been found experimentally to retard recovery following brain damage in animals.[124]

Pharmacotherapy of Mood and Behavior Disorders

Standard antidepressant and anxiolytic medications are usually efficacious for these conditions. Anxiolytics, preferably less sedating ones, should be used cautiously and usually briefly because of their euphoriant and addictive potential. Because the antidepressants, particularly those affecting serotonergic neurotransmission, are effective anxiolytics in chronic usage, a useful approach is to start an antidepressant and anxiolytic together for rapid control of anxiety then discontinue the anxiolytic in a few weeks, after the latency period of the antidepressant has ended.

Electroconvulsive therapy is particularly benign compared to drug therapy for patients with various medical conditions, and this applies as well to those with TBI. Due to legal considerations, electroconvulsive therapy is often reserved for patients unresponsive to antidepressant therapy; however, this

legal artifact should not prevent its use in cases likely to respond.

If mania occurs, mood stabilizers such as lithium, carbamazepine, or valproic acid may be used. Obviously, in mixed conditions (seizures plus mania, depression plus anxiety, depression plus pain) a single agent efficacious for both conditions may be selected.

PTSD is a common sequela not only of psychological trauma but also of physical trauma. Its treatment is described in Chapter 16, Chronic Post-Traumatic Stress Disorders. In terms of the brain-injured patient with PTSD, nonsedating agents are preferred and if a seizure disorder coexists, anticonvulsants (carbamazepine, clonazepam) should be tried first. Because clonazepam has serotonergic activity, it may be helpful through a dual mechanism.

Alcoholism, which is often associated with PTSD, poses particular problems in patients with TBI because of the intermittent withdrawal from alcohol, which is sometimes complicated by seizures. Fortunately, benzodiazepines used for withdrawal are effective anticonvulsants.

Inasmuch as aggressive behavior may be modulated through changes in a number of neuroanatomic sites and many neurotransmitter systems, including serotonin, norepinephrine, dopamine, acetylcholine, GABA and the opioids,[125] a variety of medications including neuroleptics, anticonvulsants, β-adrenergic blockers, benzodiazepines, and serotonergic agents (including lithium) may be useful in chronic aggression.[126] When aggression is severe or dangerous, neuroleptics (phenothiazines, butyrophenones, etc.) may be initially required to gain control. Neuroleptics may be helpful but the complications have been noted. Attempts should be made to replace them with more benign and often more efficacious medications such as mood stabilizers (lithium, carbamazepine, valproic acid, clonazepam, and occasionally calcium channel blockers).

β-adrenergic blocking agents (propranolol, metoprolol, etc.) have been used for decreasing aggression, particularly in patients with organic brain syndromes[127] and α-adrenergic blocking agents (clonidine) for reducing disinhibited behaviors such as sexual exposure, lewd remarks, etc. Serotonergic agents (trazodone) and benzodiazepines (lorazepam, clonazepam) have been found useful in some patients with chronic aggression.[126] Usually, treatment requires experimentation with a variety of medications until one that is efficacious is found.

Silver, Yudofsky, and Hales[128] recommend the use of propranolol in the management of the violent patient, beginning with a 20 mg thrice daily schedule and increasing it by 60 mg / d every 3 days, while monitoring blood pressure. They note that daily doses above 800 mg are not usually required and recommend that the patient should be maintained for at least 8 weeks before concluding that the medication is ineffective. In heavy smokers, atenolol may be preferable because it tends to spare the lungs; however, its latency period is longer than propranolol.

Because of success in the treatment of attention deficit and hyperactivity disorders, the use of psychostimulant drugs such as methylphenidate and amphetamine has been suggested for the management of the behavioral sequelae of TBI. Animal studies have also indicated a possible role. Dopamine agonists have been found to attenuate or abolish the septal rage syndrome, which follows lesions of the septal nuclei in rats.[129] A single dose of δ-amphetamine given 24 hours after injury has been reported as accelerating recovery of motor function after unilateral sensorimotor and bilateral frontal cortex ablation in rats and cats, an effect blocked by haloperidol given 24 hours after surgery or by restraining the animals.[130] These remarkable findings in different functional areas offered hope that stimulation of catecholaminergic systems might facilitate processes of cognitive and other behavioral recovery in TBI. To date, however, there is insufficient evidence that psychostimulants can improve brain function.

Individual case reports and anecdotal observations[131–133] have indicated that psychostimulant drugs may relieve tiredness, improve initiative and concentration, promote feelings of well-being, and result in better performance on some tests of memory and attention. The one controlled study of a case series, however, has yielded disappointing results.[134] Methylphenidate was superior to placebo but there was a marked discrepancy between subjective report and performance. Only a few objective measures showed clear stimulant effects, and there was no coherent pattern to the measures that were responsive to the drug. Patients with mild and moderate head injuries with symptoms of impulsiveness, hyperactivity, distractibility, and emotional lability may be given a trial of psychostimulants under close supervision, with consideration of the dangers of abuse, increased risk of seizures, withdrawal manifestations on cessation, and a psychotic reaction.[135]

OUTCOME

A surprisingly good overall outcome can be seen in many young, moderately severely to severely injured patients, a finding that probably reflects compensation for lost functions more than recovery of the injured tissue itself. Thus, "floating" or dynamic endpoints can be identified in the post-TBI course: recovery from coma, return of orientation, resolution of post-traumatic amnesia, shrinking of retrograde amnesia, number of significant deficits identified on initial neuropsychological testing, number of significant deficits identified on the last neuropsychological evaluation, and the steepness of the recovery slopes. Nevertheless, an important milestone yet to be reached in the TBI field is the development of reproducible, universally accepted measures of function and long-term outcome with which to compare the value of various interventions.[1]

Final outcome is a composite of a number of elements, including preinjury, neurologic, cognitive, behavioral, and psychosocial function, all of which may interact differently in each individual patient. When evaluating efficacy of a given therapy it is necessary to study all of these elements in the context of outcome as a whole; any evaluation battery should thus include at least some measure of each. It is misleading, for example, to use improvement in a particular overlearned memory task as a measure of outcome. While there may not be any ideal surrogate or summary measure for outcome, return to gainful employment may be a useful one in most TBI populations.

The second author has had the opportunity to study the disabilities that affect return to work in a large cohort (N=520) of head-injured Vietnam veterans participating in the Vietnam Head Injury Study. A 1-week, standardized, multi-disciplinary outcome evaluation was completed on each of them. Some 15 years postinjury, 56% of these men were gainfully employed, compared to 82% of an uninjured Vietnam veteran control group.[136] The occupational distribution of those who were working was essentially no different from that of normal uninjured young American males.[137] After exclusion of severe aphasic and triplegic patients, none of whom worked, a multistage statistical analysis of this data, including factor and multiple logistic regression analyses, identified seven specifically defined disabilities that had a significant impact on return to work: posttraumatic epilepsy, hemiparesis, visual field loss, verbal memory loss, visual memory loss, psychological problems, and violent behavior. Interestingly, these seven items were found to be relatively equipotent, so that a simple sum of any of them could yield a "disability score," which predicted return to work.

Patients were able to compensate relatively well for up to any three impairments, but beyond that there was a sharp drop in work rates. Other factors contributing significantly to return to work included preinjury intelligence, total brain volume loss on CT scan, and education postinjury. This experience is a further reminder of the importance of considering outcome from TBI as dependent on a set of functional skills, rather than identifying one or two disabilities as its principal determinant.

PREDICTABILITY AND PREDISPOSITION

It is difficult to predict the long-term social outcome of individual brain injuries even though the location and extent of the lesions are known. There are, however, a number of useful observations. Men whose injuries were sustained under particularly severe combat conditions, and those who have had a prior head injury or a history of combat-induced stress reactions, are apt to have more severe behavioral consequences. Injuries to other parts of the body are a factor. A follow-up study of military personnel treated at Walter Reed Army Medical Center for mainly closed-head injuries showed that patients who were violent in the acute stage and who used language of violence with references to death, blood, and mangling went on to have higher problem ratings on a scale based on employment record, social sexual adjustment, somatic symptoms, and emotional state than did men with less disturbed initial behavior.[138] Similar findings in civilian patients are reported.[139] Alcohol consumption at the time of injury is said to increase the severity and duration of initial agitation and the amount of later memory loss.[140,141] Also, premorbid personality factors may play a role. The following case is illustrative.

Case Study 3: Disastrous Social Consequences of a Brain Injury

A 44-year-old infantry commanding officer sustained a head injury and a fractured femur in a car accident while on a training exercise. His wife, who was driving, and his five children were also injured. On admission to the hospital he responded only to painful stimuli, and, because of extreme agitation, was restrained over the next 10 days. After transfer to Walter Reed Army Medical Center 6 weeks after injury, he was restless, overtalkative, tangential, and suspicious. He spoke incessantly of his children, and believed that one of them had been killed in the accident. He accused the hospital of running a dope ring and demanded an investigation.

In the first formal interview on the psychiatric ward he appeared hypomanic. He was unsure of the date, mistaken about his age (giving his wife's), and did not know the name of the hospital beyond calling it "the best hospital in the world." When asked about his accident he went into a lurid account of the consequences of nuclear and biological warfare (the subject of his course) and talked at length about his children. The RA was estimated at one half hour and the AA later determined as having endured for 7 to 10 days. His "last memory" was of scolding his wife for not having arrived to pick him up in the car. There was temporal reduplication; he stated that the examiner had given him a mental examination at Fort Benning, where the accident occurred. He admitted having suffered a head injury and a broken leg, but denied any memory loss or mental problems. He agreed that he was emotionally overstimulated and attributed this to his eagerness to see his family. He complained of blurred vision on reading, and neurological examination disclosed a partial internuclear ophthalmoplegia.

Orientation cleared over the next few days but the temporal reduplication persisted. Following a carotid angiogram, performed with some difficulty, he confabulated the next day that he had acted as defense counsel for several soldiers convicted of rape and attempted murder. He claimed that one of the men had been hanged and described in vivid detail, indicating on himself, how the man's neck had been stretched at least 18 inches. He also believed that he had been given electroconvulsive therapy (ECT).

At the time of discharge from the hospital, 4 months after his injury, the patient's mood was subdued but he would become overexuberant during testing and interviews. He was no longer confabulatory but believed that a steel plate had been placed in his head. (A pin had been inserted in his femur.) He also became preoccupied with repairing the leaky roof of the buildings on his farm. He had considered having this done prior to his injury, but had given up the idea because of the great expense. Now, however, he was determined to proceed regardless of cost. Despite the recommendation that he not resume his occupation as an agricultural administrator for several months, he insisted on returning to work immediately.

Follow-up over a 5-year period revealed a pattern of domestic and emotional difficulties. He became increasingly critical of his children and demanded perfection from them. He also projected his concerns with his own health upon them. He forbade them to watch television as it was bad for their eyes (he had some residual blurred vision), and would not allow his daughter to ride her horse for fear of a head injury. He was sexually demanding, insisting on intercourse several times a day, without any display of affection. After his wife had a hysterectomy following a hemorrhage, he accused her of evading her conjugal duties. After one of his sons drank poison in a suicidal gesture, he considered shooting himself in the head for having failed as a parent. He was technically competent on his job, but was overbearing with subordinates and charged that his secretary was talking about him behind his back. After 3 years his wife obtained a separation, and he went to live with his widowed mother and to work for his brother.

Some of the behavior was an exaggeration of premorbid personality traits. The patient had grown up in a prosperous Calvinistic work ethic family, in which the rod was not spared. His mother recalled him as a quiet, timid child who might be punished by his father for showing fear. His wife described him as a driving—and driven—perfectionistic, stubborn person, proud of his success in his several businesses and his military activities. He was the dominant member of his family, very attentive to his children and intent on making them responsible and achieving. His wife noted that he never played with them. He took pride in his good health, and regarded illness as a sign of weakness of character. He was intolerant of the ills of others, except in the case of his children, about whose even minor ailments he would become excessively worried; he was particularly unsympathetic with mental illness. He had been sexually active, and had taken any refusal by his wife as a personal rejection. Overall, he had been concerned with the physical aspects of relationships and situations with strong views of race and blood lines, looks, smells, diet, and nutrition.

Comment: The following features are noteworthy.

- Preservation of technical competence with marked disturbances in social and emotional behavior.
- Association of a long initial period of violence with an unfavorable outcome.
- Confabulation about the hanging of a deserter as a symbolic representation of the patient's traumatic carotid angiogram.
- The "last memory" prior to the injury of scolding his wife as symbolic of the patient's habitual hypercritical attitude toward her.
- The replacement of the patient's initial preoccupations and delusions about his children with a projection onto them of his own physical problems.
- A premorbid predisposition to denial and the role of denial in the patient's premature return to work.
- A possible connection between the patient's premorbid emphasis on the physical aspects of personal relationships with later paranoid attitudes, including these expressed through sex.

The mechanisms by which premorbid experience interacts with alterations in brain function following TBI are poorly understood. Most clinicians are aware of a relationship but the lack of a method of study has hampered research in the field. There are so many theories of personality that selection of measuring instruments appropriate for brain injuries is a problem.[142] Patients are often not good informants, and interviews carried out with relatives are of necessity retrospective. Another difficulty is that the life experience of a 17- or 18-year-old youth is so limited that his character cannot be fully evaluated. Some writers believe that behavioral traits such as disorderliness, argumentiveness, suspiciousness, and anxiousness become more pronounced and that extroverted patients become more boisterous.[97] However, disorderly patients may previously have been orderly, and patients with frontal lobe lesions may have deficits in executive functions and the social proprieties regardless of premorbid personality.

Another approach has been based on the idea that premorbid experience influences the positive, adaptive—or maladaptive—aspects of behavior following brain injury, as opposed to such negative symptoms as lack of empathy, loss of initiative, impaired emotional recognition, and diminished impulse control. Denial and some other delusions and confabulations are adaptive in the sense that they are attempts by the patient to cope with and interpret what has happened to him, make sense of his environment, and gain a *feeling* of reality. Interviews with relatives are directed toward learning how the patient has reacted to stress in the past, and toward determining the values through which he has structured his social environment. These values include attitudes toward health and illness, work and efficiency, physical appearance, family, sex, violence, religion, and ethnicity. Patients with marked and enduring delusional denial have been described variously as dogmatic and inflexible, highly work-oriented with emphasis on self-sufficiency, reserved with their feelings, and as regarding incapacity or illness as a personal failure.[66,143,144] Patients who had been more emotional and open with their feelings, and in whom these were expressed as "physical" symbols such as those relating to the body, looks, food, and sexual activity, were more likely to have paranoid forms of denial. Patients with violent backgrounds have been found to be predisposed to violence after brain injury.[126] As in the case described, patients who identified strongly with children and whose lives were structured in terms of a parent-child relationship may have delusions and preoccupations about children.[145] Patients who made inappropriate sexual remarks and gestures, who had delusions about sex, and who structured their problems in sexual language often had a history of hypersensitivity to the implications of sex in personal relationships and of highly stereotyped views of the roles of men and women.[146] It should be noted that these personality factors contribute to the behaviors described only after particular types of brain damage, but it is also noteworthy that patients with comparable lesions may exhibit marked differences in the cognitive and affective aspects of social behavior.

In recent years more attention has been paid to genetic and early acquired genetic factors, child abuse and possible brain damage, mental illness and alcoholism in close relatives, attention deficit and hyperactivity, and other learning disorders. Although interest in personality factors has declined, a knowledge of the premorbid personality characteristics of the brain-injured subject is of great importance in rehabilitation.[93] Discussion with a patient may help to show him how his own personality may be contributing to his failure in adaptation or conversely be helping him to adapt.

SUMMARY AND CONCLUSION

These are exciting times for the field of TBI. The understanding of the complex pathogenesis of acute TBI has grown exponentially over the past few decades with the delineation of focal injury, diffuse axonal injury (DAI), hypoxia and ischemia, and diffuse microvascular injury with loss of autoregulation. With the possible exception of DAI in penetrating brain wounds, these processes occur in both closed and penetrating head injuries. This initial brain damage is followed by secondary tissue injury at the cellular level, involving particularly oxygen free radicals, which affects otherwise viable tissue, so that much of the loss of function after TBI is not due to the injury itself but to a vicious cycle of subsequent biochemical events. Treatment, along with conventional measures to control shock and intracranial pressure and to evacuate hematomas, is aimed at the prevention and correction of secondary tissue damage. Among the more promising medical therapies now enter-

ing clinical trials are the inhibiting of lipid peroxidation with 21-amino steroids, and the control of oxygen free radicals with superoxide dismutase and catalase.

DAI has been demonstrated even after minor head injury, and occurs in the absence of morphopathological change in any other vascular, glial, or neural element. The finding establishes a possible organic base for "postconcussion syndrome," once thought to be of psychological origin.

While penetrating and closed-head injuries (CHI) share a number of pathological features, there are clinical differences. Patients with an acceleration/deceleration CHI are by definition unconscious, while those with penetrating head wounds frequently do not lose consciousness or have amnesia. Penetrating head wounds have a much higher incidence of subsequent seizures. The neurological deficits following penetrating wounds are more focal and include aphasia, lateralized motor and somatosensory loss, and visual field defects. Patients with CHI have predominant damage to frontal and temporal limbic structures and are more apt to develop impairments of memory and attention, in the perception of reality, and in social and emotional behavior. These differences are not absolute: penetrating injuries of basilar and other deep brain structures can result in prolonged unconsciousness and memory loss.

In recovery from severe head injuries, coma may be followed by a period of restlessness and agitation, and by a stage of altered interaction in the environment with features of the amnestic confabulatory state and the denial syndromes, that may endure for months. This latter stage involves not only deficits in cognition, the perception of reality and affective control, but modes of adaptation to the stresses of reduced capacity.

While long-term cognitive loss depends mainly on the location of the lesion, notably damage to the basal forebrain, changes in social and emotional behavior, such as depression and other mood changes, and aggressive acts and attitudes derive not only from lesion location, but from premorbid experience and environmental events. Return to work after penetrating wounds sustained in Vietnam was unfavorably affected by post-traumatic epilepsy, hemiparesis and visual field loss, verbal and visual memory impairment, psychological problems, and violent behavior. Changes in personality and affective relationships are less predictable.

It is doubtful if cognitive retraining can enable the damaged brain to regain lost skills. Rehabilitative measures, however, can provide the patient with a conceptual or analogical model of what has happened to him, help him to overcome denial and recognize both his deficits and remaining strengths, train him in alternate strategies, and teach him how to behave in social situations. Drugs have an important role in symptom management, in the control of disturbances of mood and behavior, in seizures, and in pain resulting from associated injuries.

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