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Review Article

Neuropathological Sequelae of Traumatic Brain Injury: Relationship to Neurochemical and Biomechanical Mechanisms

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SUMMARY: Brain injury is the leading cause of death among individuals under the age of 45 years in the United States and Europe. Recently, the neuropathologic classification of posttraumatic brain damage has provided insight into the specific mechanisms underlying traumatically induced neuronal damage and death. Studies regarding the biomechanics of brain trauma have also provided great insight into the pathophysiologic mechanisms underlying specific patterns of posttraumatic cellular death. Based upon recent clinical evaluations and biomechanical studies, laboratory models of human brain injury have been developed that faithfully reproduce a number of important features of clinical brain trauma. Biomechanical models have been used to study both the acute sequelae of brain injury and the role of neurochemical alterations in contributing to the development of secondary or delayed cellular death and damage. This report reviews and integrates the laboratory investigations linking experimental models of brain injury to clinical diagnosis and treatment. (*Lab Invest 1996, 74:315–342*)

Brain injury is the leading cause of death among individuals under the age of 45 years in the United States and Europe, with an incidence in the United States of 17 to 40 per 100,000 (Rice and MacKenzie, 1989; Sosin et al, 1989). The occurrence of traumatic brain injury (TBI) requiring hospitalization is between 2,000 and 5,000 per 100,000 people, or between 2 and 12.5 million head injuries per year (Kraus et al, 1994). The estimated cost of these injuries ranges from $1 billion to $25 billion per year (Kraus et al, 1994; Pope and Tailor, 1991). The cost to families and society is particularly high when it is considered that trauma to the central nervous system (CNS) is particularly common in young men, many of whom have young children.

Any classification of brain damage after injury to the CNS must take into account the full spectrum of clinical presentation and outcome, ranging from the patient who remains in coma from the moment of injury until death, to the patient who seems normal after the initial injury but who, as a result of a complication, subsequently dies. Clinical, neuroradiologic, and neuropathologic studies have shown that brain damage after head injury may be attributed to a variety of processes, with new information suggesting that what separates mild, moderate, and severe traumatic brain injury is not so much the nature of the lesion, but its size and distribution. Nevertheless, it is not yet clear whether a continuum from mild to severe injury truly exists, and to what extent the changes seen postmortem in fatal cases can be extrapolated to the clinical and neuroradiologic features that have been identified in those who survive head injury. This report reviews the existing classification of and mechanisms underlying the pathophysiologic sequelae of traumatic brain injury.

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Classification and Mechanisms of Brain Damage: Introduction

Recent studies have attempted to provide a neuropathologic classification of brain damage in patients who die from a closed head injury, to provide clinicopathologic correlation to the existence of primary (mechanical) and secondary (delayed nonmechanical) damage (Adams, 1992). This approach has helped to

identify potentially preventable complications in patients with a head injury who "talk and die" or "talk and deteriorate" (Marshall et al, 1983), because it is now recognized that apparently minor head injury can often activate a progressive sequence of events leading to secondary brain damage with fatal outcome or severe persistent disability (Chesnut et al, 1993; Polvishock et al, 1983; Yaghmai and Polvishock, 1992). Neuropathologic classification has categorized two main stages in the development of brain damage after injury to the head: (1) primary damage, which occurs at the moment of injury and takes the form of surface contusion and laceration, diffuse axonal injury, and intracranial hemorrhage; and (2) secondary damage, which is produced by complicating processes that are initiated at the moment of injury, but do not present clinically for a period of hours to days after injury. These include brain damage due to ischemia, swelling (edema), and alterations of the brain's endogenous neurochemical mechanisms.

A major contribution to the classification of brain injury after trauma has been the application of specialized neuroradiologic techniques including computerized tomography, magnetic resonance imaging (Teasdale et al, 1992), proton emission tomography, and single proton emission tomography (Carron et al, 1993), which provide the functional correlates of the structural damage identified using conventional histology. Such techniques have generated an alternative classification of (1) focal brain damage, which includes surface contusion and laceration, intracranial hematoma, and raised intracranial pressure; and (2) diffuse brain damage, which includes ischemic brain injury, diffuse axonal injury, and diffuse brain swelling. Whereas the basis of focal lesions can be determined with a good degree of certainty, it is more difficult to be confident about the nature of diffuse brain damage in patients who are in a coma without evidence of intracranial hematoma.

A number of clinical and laboratory studies reported over the past decade have now established that the principal mechanisms of brain damage after head injury are due either to contact or acceleration/deceleration types of injury (Gennarelli, 1994) (and vide infra). Lesions due to contact injury result from an object striking the head and are typically associated with local or regional damage, including skull fracture with or without an associated extradural hematoma, surface contusions, and intracerebral hemorrhage. In contrast, acceleration/deceleration brain injury results from unrestricted head movement in the instant after injury and leads to shear, tensile, and compressive strains. Such inertial forces are responsible for the most pronounced types of damage encountered in nonmissile head injury, including acute subdural hematoma resulting from the tearing of subdural bridging veins and widespread damage to axons (Gennarelli, 1994; Thibault and Gennarelli, 1982). It is generally agreed that the focal pathologies associated with contact are more likely to be sustained as a result of a fall, whereas the diffuse pathologies are most commonly associated with acceleration/deceleration after motor vehicle accidents. An understanding of the biomechanical events associated with traumatic brain injury are critical to the development of rational hypotheses regarding the mechanisms underlying posttraumatic neuronal cell death.

Neuropathology of Traumatic Brain Injury: Relationship to Biomechanics

The biomechanics of primary injury are intimately linked to the response of the brain to both impact forces and inertial, or acceleration, motions. With the exception of forces causing slow crush injury to the skull, each of these mechanical loading conditions occurs quickly, usually in less than 50 msec. Depending on the location, magnitude, and direction of this loading, a wide spectrum of clinically relevant brain injuries appears. This section reviews the biomechanics of focal and diffuse brain lesions and presents a summary of the investigations that have studied the role of these mechanisms for specific forms of primary brain injury. This review can be considered an introduction to more detailed reviews on the biomechanics of brain injury (Melvin, 1994; Thibault and Gennarelli, 1982), and forms a basis for explaining the neuropathology of human closed head injury as well as the pathology produced in experimental models of traumatic brain injury.

Two mechanical phenomena constitute the most common causes of primary brain injury (Fig. 1): (1) "contact effects" or the local skull distortion and propagation of stress waves through the brain from the point of impact; and (2) the movement and distortion of brain material due to inertial, or acceleration, loading. Both phenomena occur when the head is struck by a rigid or padded object (i.e., impact loading). However, only inertial effects are present when the head moves indirectly as a result of impact to another region of the body (i.e., impulsive loading). In direct head impact, there is a local bending of the skull, underlying tissue strain, and a gross movement of the brain tissue. Impulsive loading, on the other hand, does not create local contact effects, but rather produces a nonuniform distribution of pressure and tissue strain that can cause primary tissue damage.

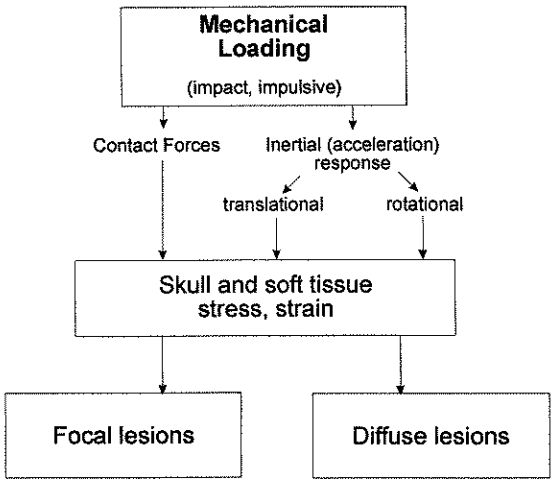

Fig. 1.
Mechanical loading characteristics such as the magnitude of impact force and rate of head acceleration strongly contribute to the type and severity of brain injury. Contact forces create focal lesions such as skull fracture, epidural hematoma, cerebral contusions, and intracerebral hematoma. Acceleration effects can cause diffuse lesions such as diffuse axonal injury, as well as numerous focal injuries.

Contact Effects and Their Resulting Neuropathologic Sequelae

Several groups over the past 100 years have examined the exact response of the skull and the underlying brain tissue to direct impact loading (Melvin, 1994). In response to relatively large impact forces, the skull deforms only slightly before fracturing due to its inherent mechanical properties. For forces distributed over very small areas, the tolerance to fracture decreases and its nature changes from a linear to a penetrating or comminuted depressed fracture (Gurdjian et al, 1949). The local depression, or inbending, of the skull from dynamic contact forces causes stress waves to propagate through the skull in all directions from the point of impact. As these waves travel and meet at points on the skull remote from impact, the addition of these skull stress waves may occur and cause skull fracture remote from the impact site. Although the exact forces that create skull fracture from either local or remote effects vary among individuals, consideration of variables such as subject age and extent of bone mineralization may prove effective in minimizing this variability (Got et al, 1983).

The local distortion of the skull without fracture can also transiently deform the underlying brain tissue and create pressure gradients throughout the brain. Mathematical models have indicated that the rate and amount of local skull displacement are important predictors of the magnitude of pressure underneath and remote from the impact site (Lee and Advani, 1975; Liu et al, 1975). In these models, due to the apparent association between skull displacement and intracranial pressures, several studies have been performed in an attempt to understand the manner in which the skull deflects in response to short and long duration impact loads. Using mechanical impedance methods, the characteristic driving force frequency was found to be an important parameter in assessing the magnitude of intracranial pressures caused solely by bending of the skull (Gurdjian, 1975). Short duration impact forces (< 2 msec) generated pressure disturbances only if the skull was allowed to accelerate.

Despite the observation of several investigators that the contact effects from impact forces can produce skull bending and intracranial pressure changes, the resulting brain injuries caused by these mechanical phenomena are restricted to focal lesions such as surface cerebral contusions, intracerebral hematomas, subdural hematomas, and epidural hematomas. Negative intracranial pressure changes have been hypothesized to be significant factors in producing cerebral contusions at the sites of impact (Ommaya et al, 1994; Smith, 1979), yet the exact pressure threshold for these contusions is not known. An intracerebral hematoma is viewed as a more extensive form of cerebral contusion, and is considered by some to be caused by negative pressures larger in magnitude than those required to cause cerebral contusions. A subdural hematoma due to local contact occurs when a skull fracture compromises the vascular network beneath the fracture site. Similarly, an epidural hematoma is not associated at all with intracranial pressure increases in 85% of cases, but is thought to occur when underlying dural vessels are torn as a result of skull fracture. In the remaining 15% of cases, fracture is not observed.

Inertial (acceleration) effects and their resulting neuropathologic sequelae. The resulting acceleration caused by impact or impulsive loading creates different mechanical effects on brain tissue. Therefore, brain lesions produced by inertial forces can be quite different from those injuries due to contact. Two forms of acceleration, translational and rotational, form the basis for most biomechanical studies aimed at defining mechanisms and tolerances of brain injury (Fig. 2). Translational acceleration produces an intracranial pressure gradient and movement of the brain relative to the inner surface of the skull. The magnitude of the peak intracranial pressure depends directly on the level of translational acceleration, whereas the amount of skull-brain movement is less sensitive to the acceleration magnitude (Hayashi, 1969). In comparison, rotational acceleration produces widespread and significant tissue strains throughout the brain. The amount of shear strain is related not only to the amount of rotational acceleration, but also to the

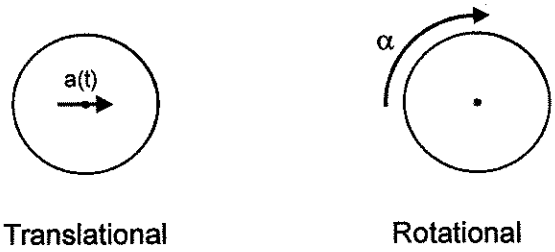

Fig. 2.
Two types of head accelerations—translational and rotational—cause most of the neuropathologic sequelae in traumatic brain injury. Translational accelerations (a(t)) move the head along a straight path, and create intracranial pressure changes with little distortion of the brain tissue. In comparison, rotational accelerations (α) cause the head to rotate, and create large intracranial motions and tissue strains.

presence of intracranial dural compartments (e.g., falx, tentorium cerebri) and direction of motion.

Initially, a great deal of attention was given to assessing the role of intracranial pressure (ICP) in brain injury. Although Denny-Brown and Russell (1941) developed an animal model that used a dynamic pressure pulse to cause concussion, they did not observe a significant correlation between ICP and damage to the brain. Subsequent studies by other investigators soon followed, however, and the causal relationship between ICP and brain damage became more apparent. Gurdjian and Lissner (1944) conducted a series of studies and found a graded distribution of pressure throughout the brain during impact, with a region of highest pressure at the impact site and a region of minimum pressure exactly opposite the site of impact. These same authors later reported data that showed the important role of duration of ICP, as well as its magnitude, in cerebral concussion (Gurdjian et al, 1953). In these studies, the magnitude of ICP required for a concussion increased as the duration of pressure decreased.

Biomechanical analyses of the effect of increases or decreases in ICP began after these initial animal studies were reported, using both cadaveric and inanimate modeling techniques. Impacts to the frontal and occipital bone of human skulls filled with water created pressure gradients that were similar in nature to those measured in animal studies. Although an impact was used to create these pressure gradients, the gradients were found to be mostly due to the acceleration or deceleration of the water-filled skull and not from the local inbending of the skull that occurred beneath the site of impact (Gurdjian and Lissner, 1961). In turn, photoelastic models constructed from surrogate skull sections were used to estimate the distribution of strain that occurred from intracranial pressures generated during vertex impacts. Results from these studies indicated a high concentration of shear strains at the craniospinal junction, a region that coincided with areas of histologic damage observed in animal head impact tests (Gurdjian and Lissner, 1961). Several investigators have also found that large negative pressures may also cause hemorrhagic lesions from fluid cavitation (Liu et al, 1975), and may have a role in deforming and moving the brain tissue during impact. However, only recently have these roles been studied critically using computational or physical modeling (Ommaya et al, 1994).

In all, the intracranial pressure changes and brain motions due to translational accelerations have been linked most extensively to lesions such as coup and contrecoup contusions, intracerebral hematomas, subdural hematoma, and histologic lesions in the brainstem region. Other lesions, however, such as diffuse axonal injury and gliding contusions, cannot be explained by the effects of translational acceleration.

In part due to the inability to explain significant neuropathologic entities, an increasing amount of focus has been placed on defining the role of rotational acceleration in traumatic brain injury. Indeed, with the exception of epidural hematoma and injuries associated with skull fracture, rotational acceleration can produce every major form of brain injury. The primary mechanism for producing this constellation of injuries is the widespread distortion and movement of the brain caused by rotational acceleration.

Evidence for the importance of rotational acceleration in brain injury first appeared in experimental studies, and was soon followed with several theoretical or computational studies. Holbourn (1943) was the first to advance an analysis that demonstrated the importance of rotational motions on brain movement and injury. Using photoelastic gelatin skulls subjected to rapid rotation without impact, it was shown that areas of high maximum shear stress coincided with brain lesions identifiable at autopsy. In contrast to the translational acceleration motions and pressures, these areas of high strain were throughout the brain and depended more on the geometric characteristics of the skull. Simple mathematic models have since aided in defining the manner in which rotational acceleration levels can cause injury to different areas of the brain, and how the duration and magnitude of acceleration may synergistically contribute to the actual locations of damage in the brain. These mathematical studies have been complemented with experimental studies that have shown significant intracranial motions can occur for a range of rotational accelerations, and these motions are relatively unaffected by adding translational accelerations to these loading conditions (Meaney et al, 1993). Moreover, recent physical modeling studies indicate that regions of the brain experi-

encing large strains during rotational accelerations may differ depending upon the direction and orientation of acceleration (Margulies et al, 1990; Meaney et al, 1993). Currently, sophisticated finite element models of the brain are being used by several groups (Willinger et al, 1992) to understand the response of the brain to impact loading, and to assist in further delineating the effects of rotational acceleration on several forms of brain injury.

In all, these biomechanical studies have yielded a considerable amount of information—not only to explain the brain lesion patterns occurring in humans, but also as a tool to study the different injury patterns produced by laboratory models of TBI. As these experimental models become more elegant and evolve to in vitro simulations, biomechanical modeling can again serve as a tool to faithfully reproduce the injury mechanisms in vitro that are responsible for the brain lesions manifest in human closed head injury.

Focal and Diffuse Brain Damage in Humans

Surface contusions and lacerations. Surface contusions, typically associated with an intact pia-arachnoid, have been considered the hallmark of brain damage due to head injury, although they may be absent in approximately 6% of fatal cases. They seem most severe on the crests of gyri and have a characteristic distribution affecting the frontal poles; the ventral aspects of the frontal lobes including the orbital gyri, the cortex above and below the Sylvian fissures, the temporal poles, and the lateral and inferior aspects of the temporal lobes; and less frequently on the ventral aspects of the cerebellar hemispheres. In the acute stages of brain injury these contusions are hemorrhagic, swollen, and may extend to involve related white matter. With time, they present as golden-brown shrunken scars and may be incidental findings in approximately 2.5% of autopsies in general hospitals.

Various types of contusions have been described, including (1) fracture contusions, which occur at the site of a fracture; (2) coup contusions, which occur at the site of impact in the absence of a fracture; (3) contrecoup contusions, which occur in the brain diametrically opposite the point of impact; and (4) herniation contusions, which occur where the medial parts of the temporal lobe make contact with the free edge of the tentorium or the cerebellar tonsils make contact with the foramen magnum at the time of injury. A fifth category, that of gliding contusions, describes hemorrhagic lesions in the cerebral cortex and subjacent white matter, and is now considered to be part of the vascular damage associated with diffuse injuries.

A contusion index has been developed that allows the depth and extent of contusions in various parts of the brain to be expressed quantitatively (Adams et al, 1985). This index has shown that severe contusions are present in approximately 10% of fatalities, moderately severe contusions in 78%, and mild contusions in 6%. More recently, a hemorrhagic lesion score has been derived which provides a finer discrimination of the distribution and severity of injury by including lesions involving corpus callosum, deep white matter, and deep grey matter (Scott et al, 1995). Lacerations are often associated with acute subdural, intracerebral, and/or intracerebellar hemorrhage, giving rise to the term "burst lobe."

Intracranial hematoma. Intracranial hemorrhage has been reported to be the most common cause of clinical morbidity and death in patients who experience a lucid cognitive interval after their injury (Bullock and Teasdale, 1990; Marshall et al, 1983). Traumatic intracranial hemorrhage may be classified as an extradural hematoma or an intradural hematoma. The effects of an intracranial hemorrhage are often delayed, because the associated brain swelling is largely responsible for subsequent secondary events, as is emphasized by the study of patients who died although they were able to talk after head injury (Marshall et al, 1983). The observation that the patients talked before death suggests that they did not have severe diffuse primary brain damage and that subsequent deterioration was a consequence of the mass effect of an expanding intracranial lesion. Although this sequence of events is particularly characteristic of extradural hematoma, some patients with an acute subdural hematoma also pursue a similar clinical course. An intracranial hematoma was present in approximately 60% of the cases in a recently published study. Moreover, extradural hematoma was present in 10% all of cases in this study and was associated with skull fracture in 85% of the adult patients. However, it is well recognized that extradural hematoma may occur in the absence of a fracture. This type of hematoma occurs most commonly in the temporal region, but in 20–30% of cases the hematoma occurs elsewhere, such as the frontal and parietal regions or within the posterior fossa (Bullock and Teasdale, 1990). Bleeding from the meningeal blood vessels causes this type of hematoma to enlarge and strip the dura from the skull, forming a circumscribed oval mass that progressively indents and flattens the adjacent brain.

Intradural hemorrhage may be subarachnoid, subdural, or intracerebral. Subarachnoid hemorrhage is common after traumatic brain injury. Subarachnoid hemorrhage resulting from trauma, as opposed to that

arising from ruptured cerebral aneurysms, is not usually associated with secondary complications of ubarachnoid hemorrhage such as hydrocephalus or vasospasm. Clinically significant subdural hematomas were observed in 18% of patients in one large clinical database, the majority of which were due to rupture of veins that bridge the subdural space where they connect the superior surfaces of the cerebral hemispheres to the sagittal sinus (Adams et al, 1985). However, some subdural hematomas seem to be arterial in origin. Attempts to classify hematomas on the basis of histologic studies have proved unsatisfactory. The current literature classifies subdural hematoma as acute when it is composed of clot and blood (usually within the first 48 hours after injury), subacute when there is a mixture of clotted and fluid blood (developing between 2 and 14 days after injury), and chronic when the hematoma is fluid (developing more than 14 days after injury) (Bullock and Teasdale, 1990). Chronic subdural hematoma occurs weeks or months after what may have seemed to be a trivial head injury, and is more common in the older age group, in which there is already some cerebral atrophy, than in younger patients. This type of hematoma becomes encapsulated and slowly increases in size, on occasion becoming large enough to produce distortion and herniation of the brain.

Intracerebral hematomas are often multiple and occur most commonly in the frontal and temporal lobes (Bullock and Teasdale, 1990; Graham et al, 1988), although they may also occur deep within the hemispheres and in the cerebellum. If a solitary hematoma is found in the brain of a patient who has suffered a head injury, the possibility that it is due to nontraumatic causes, such as hypertension or rupture of a saccular aneurysm, should be considered.

Brain damage secondary to raised ICP is a common complication in patients who sustain closed head injury, typically caused by the presence of mass lesions due to hematomas and associated brain swelling (Graham et al, 1987). An increase in the size of space-occupying lesions has been associated with deformation of brain tissue, a reduction of the volume of CSF, shift and distortion of the brain, and the formation of internal herniae. A space-occupying mass in one cerebral hemisphere may result in herniation of the cingulate gyrus beneath the free edge of the falx or herniation of the parahippocampal gyrus through the opening of the tentorium cerebelli. Within the posterior fossa, herniation of the cerebellar tonsil through the foramen magnum occurs. The basal cisterns are often obliterated by internal herniae, and pressure gradients develop between the various intracranial compartments. Eventually, these changes result in secondary damage to the brainstem, forming midline hemorrhages or infarction. Additional vascular lesions may develop, including infarction of one or both posterior cerebral arteries, the anterior choroidal arteries, and the superior cerebellar arteries. Brain damage secondary to raised ICP seems to be a common cause of morbidity and coma in patients who die within weeks of a severe head injury. Although the pathologic findings of raised ICP are present in the majority of patients who die after head injury, the most common causes of persistent disability after head injury are diffuse axonal injury and ischemic brain damage (Graham et al, 1988).

Ischemic brain damage. It has been suggested that cerebral ischemia may be one of the most important mechanisms underlying secondary brain damage associated with severe brain trauma (Miller, 1985). An understanding of the frequency and distribution of ischemic brain damage in fatal closed head injury was not reached until the 1970s (Graham et al, 1978). In this study, ischemic damage was identified in 91% (138 of 151) of a group of severely head-injured patients. The ischemic brain damage was classified as severe in 27%, moderately severe in 43%, and mild in 30% of the 138 cases, and was observed to be more prevalent in the hippocampus (81%) and in the basal ganglia (79%) than in the cerebral cortex (46%) and in the cerebellum (44%). Significant correlations were also reported between the extent of apparent ischemic brain damage and episodes of hypoxia or raised ICP. Reappraisal of the amount and distribution of ischemic damage in a second cohort of fatal, severe head injury was reported a decade later (Graham et al, 1989), after the clinical relevance of hypoxia and hypotension in the setting of traumatic brain injury had been appreciated, and revealed that ischemic damage was still present in 88% of cases.

As noted above, the most frequently involved anatomical region demonstrating hypoxic damage is the hippocampus. In a separate survey of 112 consecutive fatal human head injuries, hippocampal damage was noted in 94 cases (84%). The pattern of damage in the hippocampus resembled that seen in cardiac arrest, with the CA1 subfield being the most frequently involved (Kotapka et al, 1994). The majority (86%) of these cases also demonstrated the pathologic findings consistent with raised ICP. Thus, damage in the hippocampus in the majority of cases was thought likely to be secondary to local ischemia due to impaired cerebral perfusion secondary to raised ICP. However, a subsequent study of 14 fatal head injuries without raised ICP demonstrated hippocampal damage in 86% of cases, with the distribution of lesions again resembling that seen in cardiac arrest (Kotapka

et al, 1994). The implication of these results was that mechanisms other than ischemia could be involved in the production of such posttraumatic brain damage.

There is now considerable clinical evidence that primary traumatic brain damage may be made worse by secondary insults that occur soon after trauma, perhaps during transfer to the hospital and during subsequent treatment of the head-injured patient in the intensive-care unit. The most important predictors of mortality at 12 months postinjury have been reported to be related to the duration of hypotension or hypoxemia (Graham et al, 1989; Miller, 1985). Such secondary insults are likely to be responsible for ischemic and other forms of secondary brain damage and may be of either intracranial or systemic origin (Andrews et al, 1990). Although a number of early studies reported that pathologic evidence of hypoxia was found in 30% and arterial hypotension in 15% of comatosed head-injured patients on arrival at the emergency room, a reduction in the frequency of these early insults (Gentleman and Jennett, 1990) has recently been related to improved on-site resuscitation and transport (Andrews et al, 1990).

Although postmortem studies have indicated that there is a high incidence of histopathologic ischemic brain damage after severe head injury (Graham et al, 1978, 1989), most earlier clinical studies of acute head injury failed to demonstrate the evidence for cerebral ischemia (Enevoldsen and Jensen, 1977; Muizelaar et al, 1989; Obrist et al, 1984). However, it can be speculated that ischemia, if present, may occur in the first few hours after clinical brain injury and may not have been detected at the time the first cerebral blood flow (CBF) study was performed (Obrist et al, 1984). This possibility is supported by experimental studies that generally show the most profound decrease in regional CBF occurs in the first few hours after brain injury (Yamakami and McIntosh, 1991; Yuan et al, 1981). In studies of clinical head injury, a depression of CBF is often seen in the early hours after injury (Overgaad et al, 1981). Bouma et al (1991) reported that CBF was low during the first 6 hours after injury and found levels of CBF below the threshold for infarction (CBF $\leq$ 18 ml/100 g/min) in one-third of the CBF values obtained within 6 hours, suggesting that an acute period of ischemia does occur in a subset of severely head-injured patients. These investigators also demonstrated that a significant correlation exists between motor score and CBF in the first 8 hours after injury. Using stable Xenon-133 computerized tomography CBF measurements (Xenon-CT), Marion et al (1991) recently observed that during the first 4 hours after trauma, patients without surgical mass lesions showed a trend toward low initial flows with subsequent increase in CBF at 24 hours, and that low CBF in the first 24 hours postinjury was significantly correlated with a low initial Glasgow Coma Scale (GCS) score for patients without mass lesions. On the other hand, using single proton emission tomography, focal decreased perfusion (which may not be detected by global CBF measurement such as the Xenon-133 technique) has been reported in the acute stage of head injury (Newton et al, 1992). Taken together, these recent data indicate that either regional or global CBF reduction with subsequent ischemia might occur within the first few hours after severe brain injury, and decreased perfusion might have important effects on brain viability and subsequent neurologic status.

Global cerebral metabolic rate of oxygen is often decreased after brain trauma and has been shown to be inversely related to the severity of coma as defined by the GCS (Obrist et al, 1984). Therefore, posttraumatic oligemia might be a secondary result of impaired metabolism via normal flow-metabolism coupling, and reduced blood flow may not necessarily indicate ischemia. It has also been reported that depressed CBF later in the posttraumatic course usually reflects either low metabolic demands or brain energy failure (Bouma et al, 1991). It should be noted, however, that determination of the cerebral metabolic rate of oxygen involves the measurement of global CBF and arteriojugular venous difference in oxygen content in most studies of acute human head injury (Bouma et al, 1991; Obrist et al, 1984). In addition to the argument that jugular venous blood may not accurately represent oxygen content throughout the brain, these global measurements may not detect regional heterogenous blood flow and metabolic alterations that might occur in pathologic states such as traumatic brain injury.

Although the suggested presence of true ischemia in the acute posttraumatic period remains controversial, it is conceivable that the early postinjury period is associated with concomitant metabolic alterations that may create a "relative" ischemia in vulnerable brain regions. Using [^{14}C]2-deoxyglucose autoradiography, Yoshino et al (1991) have reported that after experimental fluid percussion brain injury in the rat, a hypermetabolic response occurs as early as 30 minutes postinjury and is resolved by 6 hours. This acute increase in glucose use and energy demand, coupled with a global hypoperfusion or oligemia, may therefore reflect a state of relative ischemia that may adversely affect ion homeostasis, membrane function, and neuronal survival.

Several factors have been postulated to contribute to the posttraumatic reduction in CBF that may lead to cerebral ischemia and infarction. These include

stretching and distortion of brain vessels as a result of mechanical displacement of brain structures (e.g., brain shift or herniation caused by intracranial hypertension), arterial hypotension after multiple injuries, vasospasm, and posttraumatic changes in the cerebral microvasculature (Bruce and Langfitt, 1976; Maxwell et al, 1988; Miller, 1985). Cerebral vasospasm has been observed angiographically after severe head injury and is implicated in the etiology of posttraumatic ischemia (MacPherson and Graham, 1978). Recently, using transcranial Doppler ultrasonography, several authors have demonstrated that a significant percentage of patients with severe head injury develop cerebral vasospasm (Weber et al, 1990). Consequently, cerebrovascular spasm is probably one of the potential mechanisms underlying the development of posttraumatic hypoperfusion states.

Pathologic changes in the microvasculature may also be associated with posttraumatic hypoperfusion. It has been shown that after acute head trauma in the nonhuman primate (Maxwell et al, 1988) and in humans (Bullock et al, 1991), microvascular collapse occurs due to swelling of perivascular astrocytic podocytic processes, suggesting that the compression of the microcirculation may cause a reduction in local tissue perfusion. With cerebral angiography, a "nonfilling" phenomenon has been observed in severely head-injured patients, and a diffuse vascular collapse produced by high ICP has been implicated in the development of such pathologic phenomena.

Diffuse axonal injury. Diffuse axonal injury (DAI) has been previously identified in 30% of cases in a clinical head trauma database (Adams et al, 1982). The presence of DAI has been commonly associated with the vegetative state and profound neurologic disability after head injury (McLellan et al, 1989). Patients with DAI form a distinct clinicopathologic group, which at the severe end of the spectrum is characterized by a decreased incidence of lucid interval, skull fracture, surface contusions, intracerebral hematoma, and elevated ICP. This type of axonal damage is particularly associated with motor vehicle accidents (Adams et al, 1982). However, evidence of DAI has also been described after traumatic assault (Graham et al, 1992) and falls from a height (Adams et al, 1984).

Early reports of posttraumatic DAI were described as "diffuse degeneration of white matter" (Strich, 1956). Since then, a variety of descriptive terms has been used, including "shearing injury" (Peerless and Newcastle, 1967), "diffuse damage of immediate impact type" (Adams et al, 1977), and "diffuse white matter shearing injury" (Zimmerman et al, 1978). In the original descriptions of severe cases of DAI, three distinctive features were emphasized: (1) a focal lesion in the corpus callosum often involving the interventricular septum and associated with some intraventricular hemorrhage; (2) a focal lesion in one or both dorsolateral quadrant(s) of the rostral brain stem; and (3) microscopic evidence of widespread damage to axons. This third, and in many respects most important feature, can only be identified histologically, and even then the appearance depends upon the length of survival of the patient. If survival is short (days), numerous axonal swellings may be seen as eosinophilic masses on nerve fibers in sections stained by hematoxylin and eosin, or as argyrophilic swellings in silver-stained preparations. They can also be demonstrated immunohistochemically (Gentleman et al, 1993; Grady et al, 1993). These axonal swellings are typically found in the white matter of the parasagittal cortex, the corpus callosum, the internal capsule, the thalami, and in the various ascending and descending tracts of the brainstem (Erb and Polvishock, 1988; Polvishock, 1992; Polvishock and Christman, 1995). If the patient survives a number of weeks, axonal swelling may persist, but the most characteristic histopathologic finding is the presence of small clusters of microglia throughout the white matter of the cerebral and cerebellar hemispheres and in the brain stem, which seem to be associated with astrocytosis and lipid-filled macrophages. The neuropathologic sequelae in patients who survive for several months or longer after the initial trauma include the presence of breakdown products of myelin in those fiber tracts in which axonal swelling and microglia are seen most frequently. Axonal bulbs may persist for up to 6 weeks, although they are most easily seen within the first 2 weeks of injury, whereas clusters of microglia seem to be most prominent between 4 and 6 weeks. In patients who survive in a vegetative state for many months or years, histologic abnormalities in the brain may include Wallerian degeneration in deep white matter. On coronal section, ventricular enlargement and focal lesions in the corpus callosum and rostral brainstem are commonly observed.

Although DAI was originally considered to be a distinct phenomenon associated only with severe brain injury, the identification of lesser degrees of DAI suggests that it is part of a continuum of diffuse brain injury, ranging from concussion to persistent posttraumatic coma (Blumbergs et al, 1989; Gennarelli, 1993b). Oppenheimer (1968) observed clusters of microglia in the brains of patients dying from an unrelated cause soon after a minor head injury. These findings were confirmed by Clark (1974), who emphasized the frequent occurrence of such clusters in the white matter of patients dying as a result of a head injury, and, more recently, by several investigators

(Blumbergs et al, 1994; Gentleman et al, 1993; Sherriff et al, 1994) who, using an antibody against β-amyloid precursor protein, presented evidence of axonal damage in patients who died from causes unrelated to a sustained head injury.

Further support for the existence of a continuum of DAI has been suggested by Adams et al (1989), resulting in the proposal of a new grading system for DAI. In Grade 1 DAI, abnormalities are limited to histologic evidence of axonal damage throughout the white matter without focal concentration in either the corpus callosum or in the brainstem. Grade 2 DAI is defined by a wider distribution of axonal injury with accompanying focal lesion in the corpus callosum, whereas Grade 3 DAI is characterized by diffuse damage to axons in the presence of focal lesions in both the corpus callosum and brainstem. The lesser degrees of axonal injury may be associated with either a complete or partial lucid interval. Because the identification of classic posttraumatic axonal bulbs using silver impregnation techniques requires an 18- to 24-hour survival in the human brain, the presence of DAI, revealed by the more sensitive technique of immunohistochemistry, suggests that the incidence of axonal injury is higher than previously published figures have reported (Adams et al, 1989; Gentleman et al, 1995). Despite significant advances in histologic identification, a definitive diagnosis of DAI cannot be made in patients who survive for only a short time (1–2 hours) after their injury—although the presence of focal lesions in the corpus callosum and the brainstem, with either gliding contusions or hematomas in the basal ganglia, are suggestive of DAI.

Experimental Models of Focal and Diffuse Brain Injury

Due to the overwhelming frequency and tragic consequences of traumatic brain injury in humans, a number of animal models have been developed to investigate specific aspects of both focal and diffuse brain injury. Although studies with physical, computer, and cell culture models have contributed greatly to our understanding of traumatic brain injury, animate models currently serve as the only true representations of a living organism's response to brain trauma. Because many of these animal models have been shown to faithfully reproduce a variety of attributes observed in the clinical setting, they have been used extensively to explore precise mechanisms leading to the sequelae of traumatic brain injury. Although the histopathologic consequences of focal and diffuse experimental brain injury are generally distinct, it should be noted that there is considerable overlap. This review is limited to models of dynamic closed-head traumatic brain injury, and will not include models of penetrating, ablation, or lesion injury; or quasistatic injury such as prolonged compression injury.

Models of focal traumatic brain injury. In the laboratory, the term "focal" is currently used to describe the primary overt pathology and circumstances of injury, such as cortical contusion resulting from a blow to the head, but does not exclude the possibility of damage remote from the primary injury. In efforts to model focal brain injury, rats have served as the species of choice (Dixon et al, 1987, 1991; Feeney et al, 1981; McIntosh et al, 1989; Nilsson et al, 1977; Shapira et al, 1988; Toulmond et al, 1993). However, several additional species have been used, including mice, cats, ferrets, nonhuman primates, and pigs (Lighthall, 1988; Lindgren and Rinder, 1965; Ommaya et al, 1966; Smith et al, 1995; Sullivan et al, 1976). These models typically employ contact loading forces to produce dynamic focal deformation of brain tissue over the course of approximately 10 to 30 msec. Although cortical contusion is the desired result in most models, some produce very little overt histopathologic damage.

Currently, three general techniques are used to produce experimental focal brain injury, viz. weight drop (Feeney et al, 1981; Nilsson et al, 1977; Shapira et al, 1998), fluid percussion (Dixon et al, 1987; Lindgren and Rinder, 1965; McIntosh et al, 1989; Toulmond et al, 1993), and rigid indentation (Dixon et al, 1991; Smith et al, 1995; Soares et al, 1992). A common feature of these models of focal brain injury is that the head is held rigidly in one position throughout the course of mechanical injury. As the name implies, weight-drop models of brain injury employ weights that are dropped through a guiding apparatus to impact either the closed cranium, a metal plate fixed to the cranium, or through a craniectomy directly onto the brain. Fluid-percussion (FP) models of brain injury use a rapid injection of fluid through a sealed port into the closed cranial cavity. Rigid indentation typically uses a pneumatically-driven impactor to deform brain tissue through a craniectomy, at a specified velocity and depth, and is commonly referred to as controlled cortical impact. Tissue deformation resulting from all three techniques may be adjusted to generate a reproducible spectrum of injury severities. Although the specific histopathology is somewhat varied between these models, several common observations have been noted that seem consistent with the clinical syndrome of focal traumatic brain injury.

Histopathology of experimental focal brain injury. Not surprisingly, the predominant histopathologic feature of these focal models of brain injury is focal contusion of the cortex (Soares et al, 1995), which is

similar to that observed in humans. Consistent with cortical contusions in the clinical setting, experimental contusions are often produced in association with a concussion of short duration (Dixon et al, 1987, 1991; McIntosh et al, 1989; Nilsson et al, 1977). Histopathologically, the contusions typically seem hemorrhagic, necrotic, and over time undergo cavitation, with their boundaries consisting of a glial limitans (Cortez et al, 1989; Soares et al, 1995). Through the use of experimental models, we have been able to discern that focal injury may actually initiate a widespread disruption of the blood-brain barrier (BBB), well beyond the contused region (Cortez et al, 1989), allowing unrestricted passage of potentially neurotoxic vascular components into brain parenchyma. Although widespread, this compromise of the BBB seems most pronounced in the region of contusion, with gradually diminishing effects in more distant structures. Posttraumatic regional cerebral edema formation, which plays an important clinical role in patient management, has also been observed after experimental models of focal brain injury (Marmarou and Shime, 1990; Soares et al, 1992; Tanno et al, 1992). Much of this edema is thought to be vasogenic, reflecting the dramatic breakdown of the BBB. In concert with these findings, decreased CBF and increased metabolism have been observed beyond contused regions in experimental models (Yamakami and McIntosh, 1991; Yoshino et al, 1991; Yuan et al, 1981). Although tissue outside the contused regions has not been shown to have a blood flow reduced below the ischemic threshold, there may actually be a "net ischemia" due to an acute superimposed hypermetabolic response to trauma. In a recent preliminary study, it has been shown that tissue loss resulting from experimental contusions produced by fluid-percussion in rats may gradually increase over time for at least 1 year after injury (Pierce et al, 1995). This may be of particular clinical importance, because brain injury in humans seems to exacerbate age-related cognitive decline and neurodegeneration (Gualtieri and Cox, 1991; Mortimer et al, 1991).

Microglial and macrophage proliferation and recruitment has been demonstrated in experimental models of focal trauma. Predominantly found at the site of maximal contusion by 72 hours after injury, microglia are also present in large numbers throughout regions demonstrating BBB disruption, including the hippocampus and thalamus (Soares et al, 1995). Astrocytosis, apparently due to hypertrophy rather than proliferation, has also been observed in many regions both proximal and distal to the site of contusion. Leukocytosis has also been observed after experimental injury in rats, initially as an increase in neutrophils that line the vasculature in the injured cortex, and that migrate into the contusion and surrounding tissue by 24 hours posttrauma, but not as widely as the glial response (Soares et al, 1995). Intraparenchymal infiltration of neutrophils is then followed by a significant increase in the presence of parenchymal macrophages (Soares et al, 1995). Furthermore, an increase in the expression of genes encoding for cytokines and other markers of injury, including heat shock protein and immediate early genes, has been demonstrated after experimental trauma (Fan et al, 1995; Raghupathi et al, 1995), suggesting that brain trauma initiates both cellular and genomic responses. These responses may be of particular importance in light of the recent evidence that brain trauma may initiate programmed cell death (apoptosis) of neurons (Rink et al, 1995).

Although it seems that the majority of damage in the contused region results from primary mechanical damage, there is evidence that pathologic changes in more distal structures may be due to a delayed or secondary insult (Pettus et al, 1994; Polvishock and Christman, 1995). As discussed in the next section, a secondary deleterious cascade of neurochemical abnormalities may selectively target vulnerable regions in the brain. The hippocampus, which seems selectively damaged in models of ischemia and seizures, has also been shown to be vulnerable in several models of experimental brain trauma (Gualtieri and Cox, 1991). This finding has important clinical implications, because cognitive impairment is the most prevalent functional deficit in head-injured patients (Levin, 1985). It has been shown experimentally, however, in a rat model of trauma, that the extent of damage to the hippocampus has been shown to correlate with the severity of posttraumatic memory dysfunction (Hicks et al, 1993). Moreover, this cognitive deficit has been shown to persist for at least 1 year after fluid-percussion brain injury in rats (Pierce et al, 1995), and may actually exacerbate cognitive decline during the aging process, in concert with clinical observations.

Damage to the hippocampus in experimental models of focal brain trauma has been reported to be primarily in the CA3 subfield and hilus of the dentate gyrus and not typically in the CA1 subfield (Cortez et al, 1989; Hicks et al, 1993; Smith et al, 1991; Soares et al, 1995), which is the most commonly damaged region after experimental ischemia. It has been suggested that this distinction may be related to the more robust cognitive deficits observed after trauma versus ischemia in humans (Smith et al, 1994b). Damage observed in the hippocampus after experimental brain injury also includes loss of microtubule associated protein 2 (MAP2) (Hicks et al, 1995; Taft et al, 1992), suggesting loss of dendritic ultrastructure in the CA3 sector. In addition, changes in receptor affinities and a

lowering of the seizure threshold in the hippocampus have been observed (Lowenstein et al, 1992), as well as induction of immediate early gene expression (Raghupathi et al, 1995).

An important "diffuse" aspect of experimental focal brain injury is the observation of widely distributed damage to axons produced by several models (Dixon et al, 1991; Polvishock and Christman, 1995; Polvishock et al, 1994). These recent findings have led to some confusion of terminology. As discussed in the previous section on human brain trauma, DAI is the hallmark of diffuse or shearing injury. However, it should be noted that the term "DAI", as used originally, refers to the clinical syndrome of prolonged unconsciousness or coma in association with a characteristic distribution of white matter tears, axonal swellings, and terminal clubbing of axons (retraction balls) (Adams et al, 1989). Therefore, the finding of damaged axons in experimental models of contusion should not necessarily be defined as DAI. The demonstration of axonal damage in regions of contusion, presumably due to primary damage, is not surprising. However, the origin of axonal injury in distant structures, such as the hippocampus and thalamus, remains unclear. Current investigations are attempting to discern whether axonal damage remote to the focal injury site is due to primary mechanical deformation or to secondary neurochemical injury. Strong evidence recently reported suggests that DAI is associated with neurofilamentous disruption and collapse of neurofilament sidearms (Christman et al, 1994; Polvishock and Christman, 1995).

An important feature of focal models of brain trauma is their use for pharmacologic evaluation. Because these models have been developed to faithfully reproduce many aspects of human brain trauma, potentially therapeutic agents may be evaluated with multiple outcome measures. A prime example is the evaluation of therapeutic efficacy of the broad spectrum excitatory amino acid receptor antagonist, kynurenate, in an experimental model of fluid-percussion brain trauma. In several studies, kynurenate therapy has been found to decrease regional cerebral edema formation, reduce changes in cation concentrations, improve neurologic motor outcome, attenuate memory dysfunction (Smith et al, 1993), decrease hypermetabolism (Kawamata et al, 1992), and reduce the number of neurons lost from the CA3 subfield of the hippocampus (Hicks et al, 1994).

Models of diffuse traumatic brain injury. Diffuse brain injuries in humans typically occur from shearing or impulsive forces, most commonly resulting from motor vehicle accidents. Through dynamic tensile strain, these shearing forces may initiate a wide disruption of white matter tracts, most commonly described as DAI. Because the majority of lesions associated with DAI are microscopic, diagnosis is based on the appearance of prolonged unconsciousness unaccompanied by an intracranial mass lesion (Gennarelli, 1993a). Shearing injury resulting in DAI has been shown to be produced primarily from high strain rotational or angular acceleration not necessarily associated with impact (Gennarelli, 1993a). Previously, only one animal model has been shown to replicate all of the clinical features of DAI. This inertial injury model, referred to as the Penn II model, was initially characterized in nonhuman primates, using nonimpact head rotational acceleration to produce coma in association with diffuse axonal damage (Gennarelli et al, 1982). The axonal damage produced by this model was found most prominently in midline structures in a similar distribution to that observed after human inertial, nonimpact brain injury (Gennarelli et al, 1982). More specifically, this model was shown to produce acute subdural hematoma (disruption of bridging vessels) and/or tissue tears in central white matter, often in association with gliding contusions in the parasagittal gray-white matter junction. DAI was found throughout the white matter of both hemispheres, the brainstem, and the cerebellum. Nonhuman primates were originally chosen for this experimental model due to their large brain mass. As described above, inertial injury in the human brain is related to its large mass, which allows for the development of high strain between regions of tissue. As the brain size decreases, the forces necessary to induce similar strains increase exponentially. To exemplify this point, the Penn II device is capable of producing 18,000 kg of thrust, just enough to generate sufficient impulsive forces (nonimpact rotational acceleration) resulting in DAI in a 50- to 75-g nonhuman primate brain.

Acceleration-induced head injury in the nonhuman primate produces a wide spectrum of pathology, the exact nature of which depends on the biomechanical profile of the injury. For example, rapid rotational acceleration in the sagittal plane produces subdural hematomas, whereas slower acceleration in the coronal plane produces diffuse axonal injury (Gennarelli et al, 1982). Both types of injury have been noted to produce contusion and hippocampal damage (Kotapka et al, 1994).

More recently, a porcine model of rotational acceleration brain injury has been developed, using young adult miniature swine (Meaney et al, 1993; Smith et al, 1994a), which have a brain mass of approximately 60 to 70 g. This new animal model was established through the initial use of physical model experiments using miniature swine skulls filled with surrogate brain

material that were subjected to scaled rotational acceleration. Analysis of point by point deformations of the surrogate brains at differing accelerations established experimental parameters predicted to produce DAI in miniature swine (Meaney et al, 1993). Subsequent experimentation with miniature swine demonstrated that rotational acceleration set at these parameters was sufficient to consistently produce axonal injury throughout the white matter, particularly subcortically. However, to date, no tissue tears or gliding contusions have been observed, and this injury is associated with only brief loss of consciousness. In the swine experiments, pure impulsive head rotation in the coronal plane was produced over 4 to 6 msec. Peak coronal plane rotational accelerations were found to range from 0.6 to 1.7 $\times$ 10^5 rad/sec^2.

An important consideration in the development of DAI is whether the damage occurs due to high strain or from ischemia superimposed on the brain trauma. Many victims of brain trauma have been shown to be hypoxic after injury and/or have reduced cerebral blood flow (vide supra). To investigate this question, the swine rotational acceleration model was used to evaluate changes in postinjury metabolism using magnetic resonance spectroscopy (MRS). Unlocalized ^{31}P MRS studies demonstrated that shortly after injury (from 30 minutes to 2 hours), only a transient decrease in the ratio of phosphocreatine to inorganic phosphate was observed, with no change in ATP or pH, suggesting that cellular energetics were not severely or irreversibly stressed. In addition, localized ^{1}H MRS studies demonstrated no accumulation of lactate in regions with decreased *N*-acetyl-aspartate concentration (a marker of neuronal injury) (Smith et al, 1994a). After histopathologic examination, these same regions were subsequently shown to have axonal damage. Furthermore, a previous study in humans demonstrated no evidence of intracellular acidosis at a mean time of 11 days after injury (Rango et al, 1990). The results from these studies suggest that DAI may indeed be produced in the absence of metabolic stress and may result predominantly from primary mechanical deformation. Although the nonhuman primate and porcine rotational acceleration models of brain injury produce axonal damage without impact, translational forces from contact loading may also initiate inertial injury leading to axonal injury, as discussed above.

Although models of focal contusion (induced through contact loading) have typically produced axonal injury that is predominantly observed proximal to the contusion site, a recently developed model of impact acceleration brain injury in rats has been shown to produce more widely distributed and more severe axonal damage (Marmarou et al, 1994). In this model, a weight is dropped onto a plate fixed to the rat's cranium. Unlike most focal brain injury models, the head is not fixed in place, but is allowed to rotate downward. It has been suggested that it is this motion, in combination with impact, that results in the overt widespread damage to axons (Marmarou et al, 1994).

Neurochemical Changes Associated with the Neuropathologic Sequelae of Focal and Diffuse Brain Injury.

Traumatic injury to the CNS causes immediate biomechanical disruption of neural pathways and vasculature (vide supra). Superimposed upon this mechanical injury, secondary neuronal or cellular damage develops over a period of hours after the initial traumatic insult. This delayed damage seems to be associated with trauma-induced neurochemical alterations, which exert pathogenic effects on brain blood flow, ion homeostasis, and metabolism; or have direct neurotoxic effects on regional populations of neurons or glial cells (McIntosh, 1994). It seems likely that these posttraumatic neurochemical changes may involve alterations in the synthesis or release of both endogenous "neuroprotective" or "autodestructive" compounds. Identification of these neurochemical cascades after brain injury provides a window of opportunity for the development of new treatments designed to prevent or attenuate neuronal damage. The following section will alphabetically review the current literature concerning the more well established neurochemical changes associated with neuronal injury after trauma to the CNS.

Acetylcholine. Elevations in brain acetylcholine (ACh) concentrations have been reported after TBI in experimental animals (Bornstein, 1946). Decreased receptor binding of cholinergic receptors has also been reported after experimental cerebral concussion (West et al, 1981). Fluid-percussion brain injury in the rat significantly decreases the affinity of muscarinic cholinergic receptor binding in hippocampus and brainstem (Lyeth et al, 1994), although in a subsequent study, Jiang et al (1994) observed that TBI significantly altered the binding sites of cholinergic receptors in hippocampus and neocortex for as long as 15 days postinjury. Activation of cholinergic pontine sites after microinjection of carbachol has been found to induce a reversible loss of consciousness/coma resembling that observed after concussion (Hayes et al, 1984), which could be antagonized by systemic or central pretreatment with the muscarinic cholinergic antagonist, atropine. Muscarinic M_1 receptor blockage has also been shown to attenuate neurologic deficits, although depletion of brain ACh concentra-

tions before fluid-percussion brain injury in the rat significantly attenuated components of transient behavioral suppression, as well as more enduring neurologic deficits (Robinson et al, 1990). Increases in thalamic ACh turnover rates and ACh content in the amygdala and cingulofrontal cortex have been reported after brain injury (Saija et al, 1989). Based upon these data, Hayes and colleagues have suggested that activation of muscarinic cholinergic systems in the rostral pons mediates behavioral suppression associated with TBI, whereas enduring behavioral deficits result from pathologic excitation of forebrain structures induced by ACh release (Lyeth and Hayes, 1992). Dixon and colleagues (1994) have recently shown that controlled cortical impact in the rat causes an impairment of cholinergic neurons, which produces enhanced vulnerability to disruption of cholinergically-mediated cognitive function. Previous studies have also observed that administration of the anticholinergic compound scopolamine will reduce neurobehavioral dysfunction after experimental brain injury in rats (Lyeth et al, 1988, 1992). Taken together, these studies support the hypothesis that some component of neurologic disturbances and, perhaps, neuronal damage after TBI, may be attributable to increased functional activity of cholinergic systems located within specific brain regions (Lyeth and Hayes, 1992).

Arachidonic acid cascade. Elevations in intracellular calcium (vide infra) will facilitate an attack on the cell membrane by calcium-activated proteases and lipases, and will also induce the formation of a variety of potentially pathogenic compounds from a breakdown of endogenous intracellular fatty acids, such as arachidonic acid. Activated phospholipase A_2, lipoxygenase, and cyclooxygenase are known to degrade arachidonic acid into the eicosanoid metabolites thromboxane A_2, prostaglandins, and leukotrienes (Leslie and Watkins, 1985). Increased phospholipase C activity has been reported after subarachnoid hemorrhage (Nakashima et al, 1993) and experimental brain trauma (Wei et al, 1982). Posttraumatic synthesis of compounds such as leukotrienes, thromboxanes, free fatty acids, or other breakdown products of the arachidonic acid cascade has been associated with neuronal death and poor outcome in models of experimental brain injury (DeWitt et al, 1988; Ellis et al, 1989; Hall, 1985; Shohami et al, 1987; Yergey and Heyes, 1990).

Catecholamine and monoamine neurotransmitters. Traumatic brain injury acutely stimulates the sympatho-adrenomedullary axis, which may mediate posttraumatic increases in ICP and blood pressure (Clifton et al, 1983; Robertson et al, 1983; Rosner, 1985). Circulating levels of norepinephrine (NE), epinephrine (E), and dopamine (DA) correlate with GCS scores in head-injured patients, and it has been suggested that circulating catecholamines such as NE may be markers of the extent of brain injury (Hamill et al, 1987). Laboratory studies of experimental brain injury in both the cat and rat have also shown that circulating E and NE increase with increasing severity of injury (Rosner, 1985).

Alterations in regional brain tissue concentrations of monoaminergic neurotransmitters have also been suggested to be a pathway involved in mediating neuronal damage after brain injury. Regional alterations in tissue concentrations of NE, DA, and E have been reported after experimental fluid percussion (McIntosh et al, 1994b) and controlled cortical impact brain injury in rats (Prasad et al, 1994), suggesting that these neurochemical changes may play a role in neuronal dysfunction and damage after trauma. Experimental cortical contusion trauma has also been shown to induce a bilateral reduction of extracellular NE levels (measured using intracerebral microdialysis) in the cerebellum (Krobert et al, 1994). Alterations in α_1-adrenergic receptor binding in injured cortex and hippocampus have also been observed after experimental lateral fluid-percussion injury in the rat (Prasad et al, 1992), and a significant and prolonged increase (up to 1 week) in hypothalamic NE and DA has been reported to occur in an identical brain injury model, possibly representing activation of noradrenergic and dopaminergic fiber tracts innervating various hypothalamic nuclei and cerebral blood vessels (McIntosh et al, 1994b). Activation of serotonergic (5-HT) systems has also been suggested to play a role in posttraumatic cerebral metabolic dysfunction (Pappius and Dadoun, 1987). Cortical 5-HT metabolism was found to increase throughout the lesioned hemisphere after unilateral hemispheric freezing injury in the rat. This increase in 5-HT was temporally related to a previously observed depression of local cerebral glucose use (Pappius, 1981). More recently, regional 5-HT synthesis was observed to significantly increase in cortical regions throughout the injured hemisphere after brain trauma (Tsuiki et al, 1995). The increase in 5-HT occurred at the time of greatest depression of glucose use, in regions showing extensive histologic damage.

Cytokines. Alterations in circulating titers of immunocompetent cells have been observed in plasma from head-injured patients (Piek et al, 1992; Quattrocchi et al, 1990, 1992), which may have direct relevance to posttraumatic neuronal damage. Because the BBB is open after brain trauma, often for extended periods, it is possible that entry of blood-borne constituents into injured brain parenchyma may be neurotoxic

(Zhuang et al, 1993). Acute polymorphonuclear leukocyte accumulation has been observed within 24 hours of brain injury (Biagas et al, 1992; Soares et al, 1995) and correlates directly with the development of posttraumatic cerebral edema in rats (Schoettle et al, 1990). Experimentally-induced neutropenia, however, was not observed to influence the development of posttraumatic cerebral edema or reduce cortical lesion volume (Uhl et al, 1994), although Chen and colleagues have shown decreased volume after MCA occlusion in immunosuppressed (neutropenic) rats (Chen et al, 1993). Macrophages have been suggested to play a major role in wound healing after penetrating brain injury (Giulian et al, 1989), and many of these immunocompetent cells secrete soluble factors, including cytokines, that may influence posttraumatic neuronal survivability and outcome. Moreover, injured neuronal and non-neuronal cells within the CNS can synthesize and secrete inflammatory cytokines that may mediate, in part, diffuse neuronal damage after CNS trauma. Among the cytokines implicated in various neuropathologic damage are TNF and the interleukin family of peptides. Elevations of plasma TNF (Goodman et al, 1990) and both plasma and ventricular interleukin-6 levels (McClain et al, 1991) have recently been reported after human head injury. After mechanical trauma to the brain, dramatic increases in regional brain concentrations of interleukin-1 and interleukin-6 have also been reported by Woodroofe and colleagues (1991). An increase in interleukin-1β and interleukin-6 mRNA, together with an upregulation of their respective receptors, has been reported after mechanical brain lesions (Yan et al, 1992). More recently, Taupin et al (1993) have observed an increase in interleukin-1, interleukin-6, and TNF levels, whereas Fan and colleagues (1995) have reported regional upregulation of IL-1β gene expression in rat brain after fluid-percussion brain injury, suggesting that these CNS-derived cytokines may play a role in the pathophysiologic cascade of brain trauma.

Endogenous opioid peptides. A significant increase in regional immunoreactivity of the endogenous opioid, dynorphin (but not leucine-enkephalin or β-endorphin), occurs after FP brain injury, which has been shown to correlate with regional histopathologic damage and reductions in regional CBF (McIntosh et al, 1987a, 1987b), suggesting that dynorphin may play a role in mediating posttraumatic neuronal injury. Both intracerebroventricular and intraparenchymal microinjections of dynorphin and other κ-agonists will exacerbate neurologic injury after fluid percussion brain trauma in rats (McIntosh et al, 1994a), whereas activation of μ-opioidergic neurons seems to be somewhat neuroprotective (Hayes et al, 1990). Alterations in regional endogenous opioid receptor binding in cortex and hippocampus have also been reported after fluid-percussion brain injury in rats (Perry et al, 1992).

Although the data from experimental brain trauma models are suggestive of the pathogenic role of dynorphin in traumatic brain injury, data from other models of CNS injury do not confirm the proposed pathogenic role of this peptide. Dynorphin 1–13 or κ-agonists have been shown to improve neurologic outcome after experimental ischemia in rats (Tang, 1985) and cats (Baskin et al, 1985). The κ-agonist U50,488H has been shown to improve spinal cord blood flow after spinal injury in cats; and improve neurologic status after concussive brain injury and reduce memory dysfunction associated with transient cerebral ischemia in mice (Hall et al, 1987; Itoh et al, 1993). Mackay et al (1993) observed neuroprotective effects after pretreatment with the κ-opioid agonist CI977 in a model of focal cerebral ischemia in the cat.

The effects of posttraumatic dynorphin release may be mediated by other neurotransmitter or neurochemical systems, including the excitatory amino acid (EAA) neurotransmitters glutamate and aspartate, which have been implicated in the pathogenesis of head injury (vide infra). Recent studies suggest that the release of EAA may contribute to dynorphin-induced neuronal damage, suggesting a potential mechanistic link between release of endogenous opioids, excitotoxicity, and posttraumatic secondary injury (Isaac et al, 1990; Shukla and Lemaire, 1995). Intrathecal dynorphin administration causes a decrease in tissue levels of glutamate, aspartate, and glycine (with a presumptive increase in extracellular concentrations of these amino acids) (Bakshi et al, 1990). Dynorphin neurotoxicity in models of spinal cord injury has been suggested to be mediated by activation of the N-methyl-D-aspartate (NMDA) receptor (Caudle and Isaac, 1988), and the paralytic effects of intrathecal dynorphin administration have been shown to be reversed by both competitive and noncompetitive NMDA antagonists (Isaac et al, 1990). Administration of NMDA-associated glycine receptor antagonists has been shown to alter the behavioral effects induced by intrathecal dynorphin injection (Bakshi and Faden, 1990), whereas the overexcitation and damage to cultured hippocampal pyramidal cells induced by endogenous opioid peptides can be antagonized by the noncompetitive NMDA antagonist magnesium (Zieglansberger et al, 1979). Other studies have demonstrated that dynorphin can substantially reduce neuronal degeneration caused by exposure of cortical cell cultures to NMDA (Choi, 1989), and can suppress glutamate-induced excitation in cultured hippocampal pyramidal cells (Moises and Walker, 1985). More re-

cently, activation of κ_2 opioid receptors has been shown to inhibit NMDA receptor-mediated synaptic currents in CA3 pyramidal cells (Caudle et al, 1994). Moreover, the neuroprotective effects of CI-977 and other κ-agonists have been related to the inhibition of glutamate release in brain slice preparations (Hayward et al, 1992; Lambert et al, 1991). Although the mechanisms by which dynorphin induces NMDA-receptor-mediated activity remain speculative, a recent report demonstrating that dynorphin administration through a microdialysis probe causes a dose-dependent increase in glutamate and aspartate suggests that opioids may modulate the presynaptic release of excitatory amino acid neurotransmitters, thereby contributing to regional neuronal damage during the acute posttraumatic period (Faden, 1992).

Excitatory amino acids. The EAA neurotransmitters glutamate and aspartate produce cell swelling, vacuolization, and neuronal death after direct application to both neurons and glia in vitro, resulting in the generation of the term "excitotoxicity" (Olney, 1969, 1971, 1987). After pathologic release of EAA neurotransmitters and activation of specific glutamate receptors, an increased neuronal influx of cations (sodium and calcium) occurs in the cell through specific ion channels, which may damage or destroy cells through direct or indirect pathways (Olney et al, 1987; Rothman and Olney, 1987). Choi has suggested that two sequential mechanisms mediate excitotoxin-induced cell death: (1) an influx of chloride and sodium, leading to acute neuronal swelling; and (2) an influx of calcium, leading to more delayed damage (Choi, 1987; Choi et al, 1987). EAA agonists such as glutamate, kainic acid (KA), or NMDA cause direct cell death when injected into the brain (Choi, 1987; Coyle and Scxhwarz, 1976), possibly via increased calcium influx (MacDermott et al, 1986), decreased high-energy phosphate stores (Hagberg et al, 1986), or free radical production (Dykens et al, 1987).

Three major classes of EAA receptors have been identified: (1) kainate/α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA/KA) receptors seem to be associated with a receptor-mediated ion channel (ionophore), which opens in a nonvoltage-dependent manner, allowing intracellular influx of monovalent cations (influx of Na^+, efflux of K^+). A subtype of these AMPA/KA receptors may exist that is permeable to Ca^{++} (Mayer and Miller, 1990); (2) NMDA receptor subtypes generate their responses via a voltage-dependent conductance mechanism (Nowak et al, 1984). The voltage-dependent blockade of receptor-linked ion channels by the magnesium ion seems to determine the involvement of NMDA receptors in pathologic processes mediated by EAA neurotransmitters (Ascher and Nowak, 1988; Johnson and Ascher, 1991; Mayer et al, 1984); (3) the EAA metabotropic receptor activates phospholipase C (PLC), which then induces the formation of intracellular inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 has been shown to release stored intracellular Ca^{++}, thus increasing intracellular free calcium ($[Ca^{++}]_i$) concentrations, whereas DAG has been shown to activate protein kinase C (Tanabe et al, 1992). Although regional distribution of NMDA and nonNMDA (AMPA/KA) receptors has been directly related to the selective vulnerability of specific brain regions to damage induced by CNS injury (Choi, 1990; Choi and Rothman, 1990), little work has been performed to characterize specific EAA receptor changes after trauma. Miller and coworkers (1990) have reported an acute decrease in NMDA, but not AMPA/KA, receptor binding in the hippocampal CA1 stratum radiatum, in the molecular layer of the dentate gyrus, and in the outer (layers 1–3) and inner (layers 5 and 6) layers of the neocortex at 3 hours after experimental FP brain injury in rats.

A number of studies have shown that experimental brain trauma induces an immediate and profound increase in extracellular EAA concentrations (Faden et al, 1989a; Katayama et al, 1990; Nilsson et al, 1990; Palmer et al, 1993). However, major discrepancies have been noted in these studies with respect to the magnitude of the posttraumatic event. Baker et al (1993) have also reported that glutamate is significantly elevated in the CSF of brain-injured patients for up to 3 days postinjury, whereas Palmer et al (1994) have reported prolonged (up to 4 days) increases in CSF glutamate concentrations after human head injury, supporting the concept that TBI involves an excitotoxic component that actively destroys populations of neurons and contributes to diffuse posttraumatic lesions.

Growth factors. The potential of neuronal and nonneuronal cells to recover from traumatic injury seems to depend both on the posttraumatic ionic/neurotransmitter environment and on the presence of neurotrophic substances (growth factors) that support neuronal survival, induce sprouting of neurites (plasticity), and facilitate the guidance of neurites to their proper target sites. The most well characterized neurotrophic factors include nerve growth factor (NGF), basic fibroblast growth factor (bFGF), brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), and NT-3. Several recent studies have suggested that neurotrophic factors are synthesized or released after traumatic CNS injury, perhaps to facilitate repair and stimulate attempts at posttraumatic regeneration (Conner et al, 1994; Hagg et al, 1994; Varon et al, 1991). Regional increases in NGF have

been reported in injured regions during the first few days after penetrating stab wound injury (Nieto-Sampedro et al, 1982), cortical ablation (Whittemore et al, 1985), or deafferentation (Needels et al, 1986). Increases in regional brain NGF concentrations have been observed in models of ischemia (Lindvall et al, 1992) and spinal cord trauma (Reynolds et al, 1991). A significant increase in mRNA for the NGF receptor has been correlated with cell survival and sprouting after fimbria-fornix lesions (Gibbs et al, 1991), whereas alterations in NGF receptors and NT-3 receptors have been observed after ischemia (Shozuhara et al, 1992; Takeda et al, 1992) and spinal cord trauma (Brunello et al, 1990). Fluid percussion brain trauma in the rat has also been shown to cause a loss of NGF receptor immunoreactive neurons in the medial septal nucleus (Leonard et al, 1994). An increase in GDNF has been observed after excitotoxin-induced destruction of the dorsal hippocampus (Bakhit et al, 1991). Basic FGF has also been observed to regionally increase after fibria-fornix lesions (Gomez-Pinilla et al, 1992), cortical lesions (Eckenstein et al, 1991), or penetrating cortical trauma (Logan et al, 1992). Although little is known concerning the neurotrophic factor response in models of experimental traumatic brain injury, NGF- and FGF-like neurotrophic activity has been observed to increase in the cerebrospinal fluid of traumatically brain-injured patients (Patterson et al, 1993). Intraparenchymal infusions of NGF over a 14 day postinjury-period have also been reported to reduce septohippocampal cellular damage and improve neurobehavioral motor and cognitive function after fluid percussion brain injury in the rat (Sinson et al, 1995).

Ion changes. **Calcium.** Changes in calcium ion homeostasis have been reported to underlie delayed neuronal death and degeneration after experimental subarachnoid hemorrhage (Hubschmann and Nathanson, 1985) and cerebral ischemia (Rappaport et al, 1987; Young et al, 1987). The distribution and binding capacity of hippocampal L-type calcium channels have been shown to be altered after experimental CNS injury (Magnoni et al, 1988), whereas immunohistochemical determination of calcium-calmodulin binding has been shown to accurately predict the existence of neuronal damage after CNS injury (Picone et al, 1989). Total brain tissue calcium concentrations have recently been found to be significantly elevated in injured areas after both experimental FP brain injury and cortical contusion in rats (Shapira et al, 1989), and significant increases in regional calcium accumulation have been shown to persist for at least 48 hours after FP brain injury in the rat (Hovda et al, 1991). Increased expression of the immediate-early genes *cfos/cjun*, heat-shock protein mRNA, calbindin-D28K, and genes for the glucose-regulated proteins grp 96 and grp 78 has been reported after FP injury in the rat (Lowenstein et al, 1994). These genes are known to be activated by increases in intracellular calcium. Increases in intracellular Ca^{2+} can also activate calcium-specific neutral proteases such as calpain, which will cause profound cytoskeletal degradation and neuronal death. Recently, Saatman and colleagues (1994, 1995) reported regional increases in calpain-induced spectrin degradation byproducts, and that administration of the calpain inhibitor AK295 will improve behavioral outcome and reduce cellular damage after lateral fluid-percussion brain trauma in the rat.

Magnesium. In the CNS, magnesium is involved in a number of critical cellular processes, including glycolysis and oxidative phosphorylation, cellular respiration, and synthesis of DNA, RNA, and protein (Aikawa, 1981; Garfinkel and Garfinkel, 1985). The presence of magnesium is also essential for mitochondrial and plasma membrane integrity (Aikawa, 1981). Magnesium regulates the maintenance of normal intracellular sodium and potassium gradients (Aikawa, 1981); alterations in tissue magnesium impair maintenance of these gradients and potentially contribute to the secondary development of ion disturbances and posttraumatic edema. Intracellular free magnesium (Mg_f) concentrations, determined from the chemical shift differences in ATP peaks (which is dependent upon the ATP and magnesium-free ATP) of a phosphorus ^{31}P NMR spectrum (Gupta et al, 1983), have been reported to be markedly and acutely decreased after lateral (parasagittal) FP brain injury in rats (Vink et al, 1988). Subsequent studies have verified that this decline in brain magnesium is a common feature after traumatic CNS injury (Vink and McIntosh, 1990; Vink et al, 1990). A reduction of cytosolic free magnesium concentrations can impair glucose utilization, energy metabolism, and protein synthesis; and can reduce both oxidative and substrate level phosphorylation, thereby contributing to regional cell death after brain trauma. Because magnesium has an important regulatory role with respect to calcium transport, accumulation, and cerebrovascular contractibility (Altura et al, 1984), alterations in intracellular magnesium could potentially contribute to posttraumatic calcium-mediated neurotoxicity or the regulation of regional posttraumatic blood flow.

Potassium. Studies employing intracerebral microdialysis have confirmed the rapid and massive release of potassium into the extracellular space after experimental brain trauma, which seems to be associated with widespread depolarization (Astrup et al, 1980; Katayama et al, 1990; Takahashi et al, 1981). After

minor concussion, potassium concentrations may range from 4 to 20 mM, but with more severe injury, may reach 50 mM (Takahashi et al, 1981). DeSalles et al (1987) have reported that cortical depolarization and posttraumatic epileptic activity after FP experimental brain injury in the cat are associated with significant increases in extracellular potassium concentrations in injured cortex (Takahashi et al, 1981).

The acute and marked release of potassium after brain trauma can induce a variety of electrical abnormalities including burst discharges, depolarization, and spreading depression (Sugaya et al, 1975; Takahashi et al, 1981); and may also cause disturbances in neuronal membrane and metabolic and synaptic function (Kimelberg et al, 1979). Posttraumatic increases in extracellular potassium have been suggested to contribute to disruption of energy homeostasis (Hansen, 1985; Kraig et al, 1983; Siesjö and Wieloch, 1985), cerebral vasoconstriction, altered cerebral glycolysis (Hegestatt et al, 1981), and loss of consciousness or autonomic function observed after brain injury.

Under normal circumstances, glial cells assist in the removal of potassium ions released from neurons during activity (Hertz, 1982). After brain injury, however, concentrations of extracellular potassium reach 10 to 50 mM and rapid uptake of potassium by astrocytes may result in intracellular swelling (status spongiosis) (Bourke et al, 1975, 1983; Kimelberg, 1979). Astrocytic edema has been reported after brain injury and stroke (Kimelberg et al, 1982). Because potassium uptake into glia is an oxygen-dependent process (Hertz et al, 1973), it is possible that the loss of potassium from neurons may further deprive traumatized neurons of their oxygen supply (Siesjö, 1981). Excess potassium can also induce the release of neurotransmitters such as adenosine or NE, which may increase the permeability of glial cells to sodium and contribute to astrocytic swelling (Bourke et al, 1981; Kimelberg, 1979a). This glial swelling may also impair neuronal oxygen transport and participate in regional anoxic neuronal damage associated with brain injury.

Oxygen free radicals and lipid peroxidation. Posttraumatic alterations in CBF seem to contribute to trauma-associated ischemia, which may then stimulate the generation of oxygen free radicals (Hall and Wolf, 1986; Kontos et al, 1985, Kontos and Povlishock, 1986). The genesis of free radicals may also be related to posttraumatic increases in intracellular calcium (mediated by activation of the NMDA receptor ionophore or voltage-sensitive calcium channels), which induce free radical release from mitochondria (Kontos, 1989). Moreover, brain kininogens and kinins have recently been shown to be elevated after experimental FP brain injury (Heizer et al, 1988). The kinins produced from these endogenous kininogens can also promote production of free radicals by stimulating cyclooxygenase-mediated metabolism of arachidonate (Ellis et al, 1987). These highly reactive free radicals can then cause peroxidative damage to membrane phospholipids and the oxidation of intracellular proteins and nucleic acids. Free reactive iron, whose generation may be associated with intraparenchymal hemorrhage, is also a catalyst for the formation of oxygen-derived free radicals. The formation of destructive oxygen free radicals has been linked to neuronal damage, which accompanies models of brain edema (Chan and Fishman, 1980, 1985), cerebral ischemia (Flamm et al, 1978; Ginsberg et al, 1988; Kontos, 1985; Lundgren et al, 1991; Traystman et al, 1991), and brain trauma (Kontos and Povlishock, 1986, Kontos, 1989; Siesjö and Wieloch, 1985).

Platelet activating factor. Platelet activating factor (PAF) is produced by a variety of cell types including basophils, polymorphonuclear leukocytes, monocytes, macrophages, endothelial cells, platelets, and neurons themselves, and can cause platelet thrombi, intravascular thrombosis, and severe ischemic tissue injury (Bourgain et al, 1985; Braquet et al, 1989; Lindsberg et al, 1990). In the CNS, neuronally released PAF can cause increases in BBB permeability, profound vasoconstriction (Armstead et al, 1988; Kochanek et al, 1988), or be directly neurotoxic (Braquet et al, 1987; Frerichs and Feuerstein, 1990; Kornecki and Ehrlich, 1988; Unterberg et al, 1986). Regional concentrations of PAF have been reported to increase as early as 5 minutes after fluid percussion brain injury (Faden et al, 1989b). PAF has also been shown to cause an increase in intracellular levels of free calcium in cultured neurons (Kornecki and Ehrlich, 1988), suggesting that this factor may be involved in posttraumatic calcium-mediated cell death.

SUMMARY

The combined studies detailed above suggest that much progress has been made over the past decade with respect to our combined understanding of the interrelationships between the biomechanical factors underlying brain trauma, the secondary or delayed neurochemical response to traumatic injury, and the resultant pattern of histopathologic damage that occurs after trauma to the CNS. As our understanding of the molecular and cellular sequelae of traumatic injury evolves, it is becoming clear that many different or distinct types of molecular and cellular events are involved in mediating or contributing to the posttraumatic pathophysiologic cascade that results in sec-

ondary brain damage. Laboratory studies must begin to examine the timing of this cascade of specific cellular and molecular events as they relate to the biomechanics of the initial injury and to the development of reproducible patterns of histologic damage, delayed cellular death, and dysfunction. The characterization of the interrelationships between these diverse secondary injury factors and specific biomechanical forces should stimulate a new conceptual framework regarding the timing and use of novel therapeutic modalities for the treatment of traumatic brain injury.

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