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Definition, Physiology, and Severity of Cerebral Concussion

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Concussion is an old term for an even older neurological disorder. In this chapter the historical evolution of the definition is developed within a context that establishes a logical background for the modern conceptualizations of the phenomenon. Understanding this context also clarifies how and why clinicians and researchers arrived at particular starting points for understanding the pathophysiology of concussion. Moreover, since multiple researchers pointed their explanatory efforts in different directions, several accurate but incomplete accounts of concussion pathophysiology developed. No unitary accounting for concussion and its phenomena yet exists. However, tracing how theory followed observation and how speculation has followed theory provides a filter for identifying knowledge that stands independent of theory. This allows greater insight into critical issues such as defining the nature and severity of concussion.

DEFINITION

Presenting a summary definition of cerebral concussion poses an interesting challenge, since so many definitions have been proffered over the years. Definition is not trivial. Definition impacts identification, diagnosis, case conceptualization, treatment, recommendations (such as return to play), and also research and theory (Ruff & Jurica, 1999).

The early medical writings that introduced the term "concussion" and its suspected neural substrates have been described in detail by Denny-

Brown and Russell (1941), Jefferson (1944), Symonds (1962), Ommaya, Rockoff, and Baldwin (1964), Peerless and Rewcastle (1967), and Shaw (2002), among others. The history of concussion definition makes for fascinating reading in and of itself. Pertinent to the present discussion is understanding that many of the issues regarding concussion that currently are debated have been controversial for decades.

For example, writers from centuries past, such as Paré, Boirel, Littré, Hunter, and Gama, are quoted as using the term *commotio* and the phrase *commotio cerebri* to describe a phenomenon in which consciousness was interrupted by a literal shaking, or physical disruption, of the brain as opposed to pathological damage (Denny-Brown & Russell, 1941). This usage set the stage for the continuing notion that concussion represented a purely functional interruption of brain activity. The definition offered by Benjamin Bell in 1787 exemplified the early conceptualizations. Bell's observations contain the essential character of many subsequent definitions. That is, regardless of the environmental cause of the head trauma, there is no penetrating injury and no obvious physical damage to the brain that can be determined grossly.

> Every affection of the head attended with stupefaction, when it appears as the consequence of external violence, and when no mark of injury is discovered, is in general supposed to proceed from commotion or concussion of the brain; by which it is meant such a derangement of this organ as obstructs its natural and usual functions, without producing such obvious effects on it, as to render it capable of having its real nature ascertained by dissection. (Bell, as cited in Peerless & Rewcastle, 1967, p. 577)

For Bell and others, this *commotio cerebri* concept was not unlike the seasonal scenes inside the small, clear plastic domes that can be shaken to produce a snow-like effect. The "snowstorm" is transient, and with the passage of time the "snow" filters to the bottom and the scene returns to normal. The snowstorm *commotio* can be repeated as frequently as desired and causes no permanent change to the structures within the scene.

Consider also the still current controversy over whether loss of consciousness (LOC) should be considered as a defining characteristic of concussion. We know from relatively recent studies that individuals may show similar clinical symptoms following a mild, closed head trauma when some have exhibited LOC and some have not (Cantu, 2001; Webbe & Barth, 2003). Originally, LOC was the most obvious sign of brain insult following head trauma, so it was useful clinically and scientifically. In formulating their definitions, some authors assumed that LOC always occurred and was a necessary

defining characteristic of concussion (e.g., Ward, 1966). Indeed, it was often the dramatic presentation regarding LOC that made concussion so interesting. The notion that an individual might be rendered unconscious—dead to the world—but then shortly thereafter pick up his or her activities as if nothing very important had happened gave rise to theories about what kind of alterations in neural processes might have occurred, and also introduced the notion that concussion not only represented the "mild" spectrum of traumatic brain injury but also was a reversible phenomenon of purely functional origin (Denny-Brown & Russell, 1941).

From Bell's description to the present, the criteria for defining concussion have evolved further. Denny-Brown had theorized that concussion had as its basis the brief disruption or interruption of neural function (presumably electrical) as a result of trauma exerted on the skull. He and his colleagues emphasized the seeming reversibility of concussion, given the theory that concussion was based upon purely physiological properties with no structural damage that would preclude a full (and fairly quick) recovery (Williams & Denny-Brown, 1941). In contrast, at about the same time, Holbourn speculated that structural alterations did occur in concussion but were not yet measurable with extant instrumentation (Holbourn, 1943). The seemingly invisible features that produced such changes in consciousness and thinking were interpreted with increasing frequency as shear-strain injuries to white matter (Peerless & Rewcastle, 1967). More recent studies with the most sensitive imaging machines have indeed detected the presence of diffuse axonal injury (DAI) following concussion (Gentry, 1994). Moreover, the studies in animals of experimentally induced concussion have uncovered a variety of histological changes—some reversible, some not (Gennarelli, 1996; Kupina, Detloff, Bobrowski, Snyder, & Hall, 2003).

The historical notion of functional impairment in the absence of structural change as a *sine qua non* for concussion no longer rings true. In addition to physiological changes that involve powerful ionic fluxes following the insult, the new generation of imaging devices can also detect subtle changes in white matter, just as Holbourn (1943) and others predicted 60 years ago (Gentry, 1994; Johnston, Ptito, Chankowsky, & Chen, 2001). Moreover, the mounting evidence for postconcussion symptoms of severe intensity, and even for relatively long symptom duration in some concussion sufferers, argues strongly for inclusion of such phenomena in the basic definition. In his oration to the Medical Society of London in 1924, Trotter remonstrated that "seriously disabling headache is a common sequel to head injuries of an apparently minor kind, in which evidence of any direct local injury of the brain has been altogether lacking" (Trotter, 1924, p. 935). Nonetheless,

Trotter conveyed no such symptomatic message in his own definition. But Gronwall (1991) expressed the full core of the concussion concept quite well when she said:

> Basically, however, an MHI [minor head injury] is defined negatively; it is one that is not severe, that is at the opposite end of the continuum from the very serious. It is also an injury in which head trauma is not followed by abnormal neurological signs, though it can be and often is followed by complaints of headache, poor memory, impaired concentration, vertigo, irritability, sensitivity to light and noise, and easy fatigue. (p. 254)

The notion of inclusion of more than immediate symptoms is no trivial matter. As Hovda and colleagues have so elegantly described (and as will be discussed later), physiological and morphological changes may continue for many days or weeks following a single concussive event (Hovda et al., 1999). Given such knowledge, a definition that omits this temporal extension would be faulty. In addition, it is now known that postconcussion physical and cognitive symptoms may endure for very long periods in some individuals. It is just not clear how widespread this temporal extension may be (Bernstein, 1999; Moser & Schatz, 2002).

So, our working definition appears very similar to Gronwall's (1991). *Cerebral concussion is a closed head injury that represents a usually transient alteration in normal consciousness and brain processes as a result of traumatic insult to the brain. The alterations may include loss of consciousness, amnesia, impairment of reflex activity, and confusion regarding orientation. Although most symptoms resolve within a few days in the majority of cases, some physical symptoms such as headache, and cognitive symptoms such as memory dysfunction, may persist for an undetermined time.*

BIOMECHANICS

Cerebral concussion may result either from direct impact or from impulse insults to the head. These assaults neither penetrate nor fracture the skull. Impact injuries occur when an object of measurable mass strikes the skull. The impact dynamics are such that the mass of the striking object interacts with the force of propulsion so as to impart kinetic energy to the skull and thence to the brain. In the majority of such cases, the resulting energy transfer accelerates first the skull and then the brain. Impact injuries of this type typically produce focal effects. That is, the surface area of the cerebral cortex beneath the impact point on the skull may sustain impairment—a coup injury. When the acceleration of the brain is abruptly halted by the skull

opposite to the point of original impact, further injury may occur—the counter coup. The greatest risk of injury from impact forces stems from collision of the brain tissue with the bony protuberances of the skull, particularly those that impact the ventral surface of the temporal and frontal lobes (Bailes & Cantu, 2001).

Impulse injuries occur also in the absence of impact to the head. Instead, they result from abrupt changes in head movement, that is, acceleration—deceleration without impact. The absence of impact in impulse injuries may mislead an observer into concluding that severity must be less. That turns out not to be true (Barth, Freeman, Broshek, & Varney, 2001).

Linear Force

In addition to considering the category of impact versus impulse, it also is critical to assess the vector outcome of the application of force to the skull and brain. Two basic types of force application are at issue: linear (translational) versus rotational (angular). An inertial force applied linearly to the skull will impart acceleration in a straight line. Examples of a linearly applied force within this context would be a direct blow to the face or abrupt stopping of forward movement by collision with a goalpost. This will commonly result in the occurrence of the coup, and possibly counter coup, injuries just described. The resulting effects on brain tissue are likely to be primarily compression and possibly stretching. Not all combinations of force and mass will produce the same outcomes. For example, the impact of an object of very small mass at high acceleration is most likely to penetrate the skull, causing local, even mortal, damage along the path of travel but not necessarily producing the common symptoms of concussion. On the other hand, an object of great mass that strikes with low force may crush the skull, but little or no acceleration is imparted, and no concussion occurs. Thus, some intermediate values of mass and force are usually the culprits when it comes to producing concussions. A good example is a hockey stick that strikes a player's head or the sudden deceleration of the head during a motor vehicle accident, even when the air bag deploys properly.

Gurdjian (1972a), particularly, has championed the notion that compression (depression) of the skull without fracture represents an important mechanism in concussion. According to this approach, focal injury from translational forces that depress the skull without causing fracture establishes a rapid decrease in intracranial volume with an accompanying increase in pressure. Since the brain, meninges, cerebrospinal system, and vasculature constitute a closed, predominantly fluid system, the resulting pressure wave sweeps through the cranium, causing both general and local deformation of

tissue, and potential compromise of the histological integrity of nerve cells (Gurdjian, 1972a).

Rotational Force

With rotational forces, two types of injury can be seen. One is a shearing or tearing, the other is stretching or tensile (Holbourn, 1943). In a rotational injury, inertial force is imparted to the head in such a manner that an angular acceleration of the head (and brain) occurs around the midline axis. Because of the morphological connections among bone, connective tissue, and muscle in the neck and upper torso, it is much more likely that the rotational acceleration that produces concussion will be directed from the side (laterally). Thus, the midline extension of the neck up through the top of the skull represents the most common axis. Rotational accelerations may also be generated from applications of force in a straight line to the forehead or occiput, but the rigid control of the skull from musculature extending up from the trunk provides a functionally greater mass that distributes the kinetic energy and dampens the force that is applied in a front-to-back direction. Thus, it is when the skull and the brain are accelerated around the midline axis by an angular force that shear-strain injuries are most probable. With concussion, it is assumed generally that any actual shearing of tissue occurs at the histological rather than the gross level (Ommaya & Gennarelli, 1974).

As early as the 1940s, Denny-Brown and Russell (1941) and Holbourn (1943) concluded that a rotational force rather than a translational force was necessary to produce the phenomena of concussion. In his shear-strain model, for example, Holbourn viewed concussion as a disruption in cytoarchitecture within the brain as opposed to a focal injury, which was considered more likely to produce contusions. "Shear-strain, or slide, is the type of deformation which occurs in a pack of cards, when it is deformed from a neat rectangular pile into an oblique-angled pile" (Holbourn, 1943, p. 438). That conclusion was supported experimentally by Ommaya and Gennarelli (1974) more than a quarter of a century later. They reported that only rotational as opposed to linear acceleration caused loss of consciousness in their primate subjects. Injury resulting from angular acceleration or rotational forces will be most prominent at areas of gray–white tissue differentiation beginning below cortical levels and then descending deeper toward the brainstem (Holbourn, 1943; Ommaya et al., 1964; Ommaya & Gennarelli, 1974). Most typically, such damage to the white matter is referred to as diffuse axonal injury.

PATHOPHYSIOLOGY

Global Theories

Shaw (2002) has organized and commented on five historic pathophysiological theories that have been proposed over the years to underlie the symptoms of concussion. The critical issues that he discussed assist admirably in the attempt to settle on a theory that best fits the data. Not the least of the issues at hand is how the insult to the functioning of the brain accounts both for the immediate occurrence of LOC—usually considered a brainstem phenomenon—and also symptoms such as amnesia—usually considered a cortical phenomenon. It is useful to review these theories briefly to highlight the schemata into which the results of current pathophysiological studies may fit. Most of the relevant background studies stem from animal experimentation using various apparatuses to induce concussion.

Vascular Theory

This elder statesman among the formal attempts to explain concussion has been passé for more than half a century. However, in its time, this theory represented a significant advance in thinking from the simplistic *commotio* approach that specified concussion vaguely as an insult due to shaking or vibration of the brain as a whole. Since the early writers had no ability to detect any morphological or physiological changes attendant upon brain insult, they concentrated on what they could measure. Thus, the genesis of the vascular theory can be tied to the very large and obvious increase in blood pressure that accompanies concussion (and even some subconcussive blows) (Denny-Brown & Russell, 1941). Since the proposed mechanism of this hypertensive effect is vasoconstriction, the loss of consciousness and other phenomena were described as due to a brief period of cerebral ischemia, possibly due to vasospasm or vasoparalysis, or even obstruction of cerebral blood flow (CBF), which itself may increase intracranial pressure (ICP; Symonds, 1935, 1962). The vascular theory could not account for the *sudden* onset of LOC and other symptoms (Denny-Brown & Russell, 1941). That is, these vasoactive phenomena and the proposed cascade of after-effects occur too slowly to account for the immediate clinical symptoms. Moreover, the decreased energy output in the brain implied by the reduction in vascular activity has not been reported in studies of experimental concussion (Nilsson & Ponton, 1977). Ommaya and colleagues (1964) suggested that vasoactive phenomena may still be useful in describing some posttraumatic concussion effects such as amnesia. Indeed, there are robust findings of a decrease in CBF

following concussion, and vasospasm still stands as a possible mechanism to explain this phenomenon (Yuan, Prough, Smith, & Dewitt, 1988).

Reticular Theory

Once the role of the brainstem reticular formation (BSRF) in regulating consciousness was known, it made sense to link BSRF functioning to concussion since LOC was the original defining characteristic. Denny-Brown and Russell (1941) and others made such a link. Moreover, a focus on the BSRF aids in explaining the deficits in reflex behavior that are seen commonly in concussion. A reticular theory of concussion must of necessity postulate that a blow or impulse causes a reversible interruption to reticular activity, since consciousness, if lost, usually returns quickly (Foltz & Schmidt, 1956; Foltz, Jenker, & Ward, 1953). Neuropathology studies have also supported a role of brainstem (and likely reticular) involvement in concussion. The common finding of chromatolysis in the brainstem following experimentally induced concussion suggests that neuronal-destroying processes are at work. (Chromatolysis is disintegration of the granules of the Nissl bodies and is associated with structural trauma to the neuron.) Moreover, traumatic damage to brainstem axons has been noted in rats (Povlishock, Becker, Cheng, & Vaughan, 1983) and monkeys (Jane, Steward, & Gennarelli, 1985) following experimentally induced concussion, and in humans following accidental mild head injury (Oppenheimer, 1968). The obvious source of brainstem trauma would be the flexion of the brainstem structures during the peak rotational acceleration about the cervicomedullary junction (Shaw, 2002). The stretching and possible shearing of the tissue would likely cause massive functional failures. Friede (1961) suggested that such stretching might engender global depolarization of the basal reticular cells, leading to a burst of activity followed immediately by failure of the ascending reticular activating system (ARAS), and possibly even causing convulsive activity. Although the reticular theory accounts rather well for the immediate symptoms of concussion, the cognitive symptoms such as traumatic amnesia prove more problematic and are not adequately addressed.

Centripetal Theory

Ommaya and Gennarelli (1974) are most identified with this approach that combined historical theories and experimental data in showing that rotational as opposed to linear accelerations were most responsible for causing concussions. The working hypothesis that they determined was that cerebral concussion would then be defined as

> a graded set of clinical syndromes following head injury wherein increasing severity of disturbance in level and content of consciousness is caused by mechanically induced strains affecting the brain in a centripetal sequence of disruptive effect on function and structure. The effects of this sequence always begin at the surfaces of the brain in the mild cases and extend inwards to affect the diencephalic–mesencephalic core at the most severe levels of trauma. (pp. 637–638)

In relating their hypothesis to their definition of consciousness, Ommaya and Gennarelli proceeded to formulate an early grading system for concussion. What is interesting about their hypothesis and their grading system was that cortical effects were considered to be the hallmarks of *mild* concussion, whereas the dramatic brainstem effects such as LOC would occur only after rather severe trauma. This theory supported the rationale that LOC per se, and also duration of LOC, was a marker of severity in concussion. Shaw (2002) comments that this theory failed by attempting to account for both the cortical and brainstem effects with the one centripetal mechanism. Too many noteworthy clinical examples of LOC with few, if any, cortical-cognitive after-effects have been reported to allow this theory to stand without significant modification. Indeed, the disconnect between LOC and concussion severity in clinical cases was commented on in the 1930s by Symonds (1935).

Pontine Cholinergic Theory

Similar to the reticular theory, the pontine cholinergic theory (PC) posited that concussion is essentially a brainstem phenomenon. The main difference between this approach and the reticular theory is that the PC theory suggested that the brain insult *activates* an inhibitory or depressive system, whereas the reticular theory suggested a *depression* of the ARAS (Hayes, Lyeth, & Jenkins, 1989). Specifically, the pontine cholinergic theory asserted that the concussive insult initiates events that excite an inhibitory cholinergic system located in the dorsal pontine tegmentum. When the neurons served by the cholinergic synapses are thus inhibited, consciousness is reduced either somewhat or to a vegetative state, depending upon the severity of the original insult. Although research aimed to elaborate the PC theory sometimes supported the existence of such a mechanism in concussion, several studies reported problematic outcomes. The most serious challenge came from studies that showed the maintenance of many concussive symptoms following pretreatment with a cholinergic antagonist. Clearly, if concussion has a primary excitatory cholinergic component, blocking acetylcholine should

have prevented many or most concussive symptoms. This did not happen (Lyeth et al., 1988). Nonetheless, as Shaw (2002) concluded, a value of this line of work has been to stimulate a rethinking of brainstem versus cortical involvement in concussion.

The Convulsive Hypothesis

This final approach notes the similarities present with concussion and generalized epileptic seizures, and with concussion and electroconvulsive shock effects. This convulsive hypothesis can be dated most directly to Walker's work in the 1940s (Walker, Kollros, & Case, 1944), although Symonds (1935) had commented earlier that concussion and convulsion were often similar. From a simplistic viewpoint, it is asserted that since concussion and epileptic seizures appear to share qualitative commonalities, then they may share also a common pathophysiological mechanism. Shaw (2002) summarized the following similarities in physical and cognitive symptoms of concussion with epilepsy: (1) transient LOC; (2) often a sudden recovery of the senses; (3) a period of drowsiness, stupor, and disorientation; (4) depression of reflexes; (5) pupillary dilation; (6) transient respiratory arrest or apnea; (7) posttrauma hypertension; (8) acute slowing of the heart rate; (9) autonomic symptoms such as vomiting; (10) postconcussive or postictal headache; (11) tongue biting or tongue lacerations; (12) retrograde and anterograde amnesia; and (13) postconcussion or postseizure personality and cognitive changes. Individual incidents of concussion or epileptic seizure will be absent many of these phenomena, and some of the comparisons seem forced. Moreover, the comparisons often juxtaposed human seizure cases with animal experimental concussion studies that themselves had employed many differing methodological and measurement techniques (Walker, 1994). Nonetheless, there does appear to be a striking commonality of symptoms. Shaw (2002) presents considerable electroencephalographic (EEG) and evoked potential (EP) data to support the convulsive hypothesis.

Summary of Historical Theories

Obviously the major thrust involved in the research spawned by these various hypotheses and theories has been to arrive at an explanation that best models the known data regarding concussion. The difficulty of the effort is that there are so many conflicting data. If one considers only the animal experimental concussion literature, there is disagreement on such basic issues as whether the immediate effect of a traumatic incident to the brain is excitatory or depressive! However, before one throws in the towel, it should be remem-

bered that the procedures used to induce experimental concussion have not been uniform, or even adequately described within articles. For example, some studies have used a non-penetrating blow to the skull; others have used a fluid percussion procedure to deliver a percussion wave to the brain through a burr hole in the skull. With the human data, the disparate events that have created the concussions that have been the source of study include motor vehicle accidents, missile wounds, and sport-related contact and collisions. The good news even in the face of conflicting data is that some excellent research has produced considerable advances in our knowledge about the pathophysiology of concussion. We just have not yet put all the pieces of the puzzle together, possibly because the schemata holding the various theories in place are themselves not yet complete.

The following is what appears to be solid. First, mechanisms that produce LOC probably are different from those that produce amnesia and other postconcussion symptoms. The most parsimonious mechanism for LOC is a brainstem or reticular mechanism. The immediacy of LOC, when it occurs, is most consistent with such a locus. Moreover, the many articles now published which document that concussion frequently occurs with an absence of LOC argue for separate phenomena (Cantu, 2001; Erlanger et al., 2003; Guskiewicz et al., 2003; Powell & Barber-Foss, 1999). The question that has not been answered relates to whether one wants to hold onto LOC as a defining characteristic of concussion versus one possible symptomatic expression, and whether LOC relates ultimately to the severity of concussion and is predictive of postconcussive symptomatology. In answering that question it may be necessary to speculate, as did McCrory (2001), on the probability that two different kinds of concussion exist: a "brainstem concussion" and a "cortical concussion." Such a division would certainly help in understanding the conflicting pathophysiological data described above and also in making sense out of the systems proposed to grade the severity of concussion.

Summary of Current Knowledge of Pathophysiology

In 1944, Walker, Kollros, and Case wrote the following description of the sequence of events in experimental concussion:

> At the moment of concussion a marked electrical discharge occurs within the central nervous system. In the vinethane–novocaine anesthetized animal the cortical activity is increased in frequency following the initial discharge (after discharge) for 10 to 20 seconds, and then decreases until there is little spontaneous activity (extinction). Within several minutes the electroencephalogram becomes practically normal again.

> At the moment of a blow on the skull a sudden increase in pressure at the site of impact occurs with pressure waves being transmitted throughout the intracranial cavity.
>
> It is concluded that these mechanical forces produce a breakdown of the polarized cell membranes of many neurones in the central nervous system, thus discharging their axones. This intense traumatic excitation is followed by the same electroencephalographic, chemical and clinical phenomena which characterize intense stimulation of the nervous system by electrical, chemical or other agents. (p. 115)

Thus, 60 years ago, Walker and colleagues established a basic framework for considering the pathophysiological changes of concussion. Where they left off, however, was in identifying and predicting only the physiological effects. More recent research has gone onto document morphological changes in neurons and axons as well, some temporary and some permanent. Sequences and timelines of events can now be much better specified, with accurate documentation of the electrical, chemical, and morphological effects. The usual cautionary statement that the animal studies may not mirror human phenomena should be emphasized. However, there is no necessary reason that the human pathophysiology *must* be very different.

Sequential Overview of Events after Brain Trauma

At the moment of insult, the (usually rotational) force that affects the skull and brain causes immediate increases in blood pressure and decreases in cerebral blood flow. The acceleration-induced pressure wave within the skull produces differential shear of tissue (e.g., white vs. gray matter), which causes cytoarchitectural changes, including the opening of normally voltage-dependent ion channels. The ensuing flux of ions causes massive neuronal depolarization, which liberates large amounts of excitatory amino acid transmitters. The excitatory effect that ensues provides positive feedback to maintain the ionic fluxes, especially the efflux of potassium and the influx of calcium into the neurons. A hypermetabolic state ensues as sodium and potassium pumps consume incredible amounts of ATP and oxygen as they work overtime to overcome the out-of-control fluxes. Unfortunately, because of the decrease in CBF, supplies of glucose run short. Moreover, the calcium influx ultimately impairs mitochondrial function, so energy production plummets. Thus, the brain rides a roller coaster of acute excitation and hypermetabolism before falling into a state of metabolic depression, which may persist for several days after a single event. Although the persistent

hypometabolism is assumed to be a cause of impaired cognition, the acute effect does not appear to correlate with posttrauma scores on the Glasgow Coma Scale (Bergsneider et al., 2000).

Cerebral Blood Flow

Yuan and colleagues' (1988) study provided an excellent overview of the changes in cerebral blood flow. Fluid percussion impact insults in rats initiated an immediate increase in mean arterial blood pressure of 64%. This change persisted for 30 ± 11 seconds. A return to baseline levels of blood pressure was observed within 6–8 minutes. The mechanisms of this vasoconstrictive effect likely included vasospasm, reduction in nitric oxide (NO) or NO synthase activity, or the release and action of vasoconstrictive agents such as neuropeptide Y and endothelins (Yuan et al., 1988). These changes in blood pressure reported by Yuan et al. appear to be quite robust across studies (Hovda et al., 1999). Over a 1-hour period, CBF decreased progressively to about 65% of the baseline control levels, which was about 40% of the control group (the halothane anesthetic employed is a potent vasodilator, so control group CBF actually increased, the typical effect). Yuan et al. acknowledged that hemorrhage-induced increases in intracranial pressure could have compromised the CBF findings. However, they concluded that the most likely mechanism of reduction was the trauma-mediated release of prostaglandins and the subsequent prostaglandin-induced changes in cerebral vascular resistance.

Ionic Fluxes

The impact and impulse injuries that produce concussion have been shown to disrupt cytoarchitecture, particularly somatic and axonal membranes, causing neuronal depolarizations and also the opening of voltage-dependent potassium (K^+) channels (Katayama, Becker, Tamura, & Hovda, 1990). This direct effect on axonal membranes has been shown to last for up to 6 hours, during which normally voltage-dependent channels readily allow fluxes of ions including sodium, potassium, and calcium (Pettus, Christman, Giebel, & Povlishock, 1994). As a result of the depolarizations, elevated levels of excitatory amino acids (EAAs) occur, notably glutamate. These neurotransmitters activate *N*-methyl-D-aspartate (NMDA) and other receptors, which further induce the influx of sodium and calcium ions and also further increase the extracellular K^+ concentration (Okonkwo & Stone, 2003).

Glucose Metabolism

The huge increase in glucose metabolism following experimental concussion appears to be the result of a corrective mechanism. Specifically, the sodium-potassium pumps in the axonal membranes attempt to compensate for the out-of-control ionic fluxes, and demand vast glucose and oxidative energy (Giza & Hovda, 2001; Hovda et al., 1999). The demands rapidly outpace the supply, and beginning about 6 hours after a diffuse fluid percussion insult in rats, many regions of the brain enter a state of hypometabolism that lasts up to 10 days (Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). This continued hypometabolic state places the organism at great risk in the event of a second insult, since the brain may be incapable of dealing with the decreased CBF and hypermetabolic phenomena of the second concussion (Giza & Hovda, 2001). Recognition of the physiological demands of the second concussion overlaid on the first—the second-impact syndrome (Saunders & Harbaugh, 1984)—may be of critical importance when it comes to determining safe levels of activity following a concussion, including and especially return-to-play decisions in sport.

Electrical Changes

Acute changes in brain electrical activity after concussion have been studied for many years. Unfortunately, the different outcomes reported in two classic studies kindled a continuing controversy over whether the immediate effect of concussion is a general depression (Williams & Denny-Brown, 1941) versus an excitation of EEG (Walker et al., 1944). Shaw (2002) suggested that effects of anesthetic and anticonvulsant drugs likely accounted for the depressive effects seen by Williams and Denny-Brown and other researchers. However, Walker et al. and others who showed excitatory effects used similar anesthetic agents, so the lack of consistency appears to have a broader genesis. Moreover, other researchers who have used awake animals nonetheless reported an acute depression of EEG in both rats (West, Parkinson, & Havlicek, 1982) and cats (Sullivan et al., 1976). Other methodological differences also may have considerable impact on reliability and validity. These include at a minimum whether the head of the organism is confined or freely movable, the nature of the impact or impulse trauma, and a history of previous concussions. Fortunately, whether the immediate effect is excitatory or depressive, there appears to be consensus that past that point an overall depression in cerebral electrical activity ensues followed by a gradual return to normal levels over a period of several hours (Sullivan et al., 1976; West et

al., 1982; Yuan et al., 1988). Studies that have attempted to measure human EEG changes as soon after a concussion as possible (i.e., in boxing) represent valiant attempts but have encountered such methodological challenges that no reliable conclusions have been drawn (e.g., Kaplan & Browder, 1954).

Secondary Mechanisms of Injury

In addition to the immediate primary changes in CBF, ionic activity, electrical activity, and EAA-induced neurotoxicity, several other intracellular phenomena secondary to the traumatic injury have been associated with experimentally induced concussion. These include lipid peroxidation, mitochondrial swelling and damage, and initiation of apoptotic processes (Okonkwo & Stone, 2003).

Lipid peroxidation implies the degenerative action of free-radical species of oxygen on fatty membranes. Such reactive oxygen species proliferate with increases in cellular energy utilization such as occurs in the aftermath of the brain insult. In attacking cellular membranes, free radicals contribute to the prolongation of the morphological change in the neurons and axons.

The energy-producing reactions that are exacerbated following concussion take place in the mitochondria of the neurons. Moreover, it has been established that mitochondrial swelling is an early marker of traumatic damage to axons (Pettus et al., 1994). Although the influx of calcium ions (Ca^{++}) first into the axon and then into mitochondria is a likely source for early physiological disruption of neuronal activity, it appears that Ca^{++} overload in mitochondria may not directly produce long-term morphological change (Giza & Hovda, 2001). It is noted also that increasing free magnesium concentration may ameliorate that calcium overload.

Gender Differences in Pathophysiology

For several years, morphological, physiological, and hormonal data have accumulated that predict differential outcomes of concussion in males and females (Broshek et al., 2005). For example, cortical neuronal densities are greater in males, while neuropil count (neuronal processes) is greater in females (de Courten-Myers, 1999; Rabinowicz, Dean, Petetot, & de Courten-Myers, 1999). General cerebral blood flow rates are greater in females than in males (Esposito, Van Horn, Weinberger, & Berman, 1996). Although Andreason, Zametkin, Guo, Baldwin, and Cohen (1992) have suggested that females exhibit a higher basal rate of glucose metabolism (CMRglu) than males, their findings are contradicted elsewhere (Azari et al., 1992; Miura et

al., 1990). A greater CBF and (possibly) CMRglu might exist to support increased ionic fluxes across the greater membrane area suggested by the higher neuropil count. To the extent that female brains may have higher cortical metabolic demands, a more intense and prolonged symptom response to mild TBI may reflect an exacerbated metabolic cascade, as described by Hovda and colleagues (Giza & Hovda, 2001). Specifically, the typical decrease in cerebral blood flow along with the increased glycemic demands caused by TBI may interact with the already increased demands and result in greater potential impairment in females than in males. Kupina et al. (2003) have noted that the time course of neuronal cytoskeletal degradation in mice following impact acceleration injury also varies between males and females. The peak degradation occurs within 3 days in males but not until 14 days in females. Although absolute peaks were higher in males than females, the extended time course for structural flux in females suggests both a greater opportunity for effective intervention and a longer window of vulnerability.

The effect of female sex steroid hormones on survival and physiological response after TBI has been assessed almost exclusively in animals. Estrogen usually appears to have protective effects (Kupina et al., 2003; Roof & Hall, 2000b) regarding both mortality and underlying functional mechanisms. For example, estrogen commonly improves cerebral perfusion, possibly through facilitation of nitric oxide or nitric oxide synthase mechanisms (Roof & Hall, 2000a). Estrogen also has significant antioxidant effects, which may combat the destructive lipid peroxidation that follows TBI. Finally, estrogen may also reduce the excitotoxic glutamate effects at NMDA receptors, which would mitigate the immediate effects of trauma. In contrast to these common findings, Emerson, Headrick, and Vink (1993) reported that females fared worse than males following experimentally induced concussion. That is, mortality was higher in females, who also exhibited no change in free magnesium concentrations versus controls, whereas males showed an increase. Supporting a wait-and-see approach also are contradictions in human studies that evaluated individuals' recovery from TBI. In their meta-analysis, Farace and Alves (2000) reported that females were at greater risk in recovering from TBI, as opposed to Groswasser and colleagues, who reported that women in their study fared better than men (Groswasser, Cohen, & Keren, 1998).

Progesterone also appears to function broadly to reduce post-TBI neural impairment, most likely by inhibiting lipid peroxidation and the resulting vasogenic edema (Roof, Duvdevani, & Stein, 1993; Roof & Hall, 2000a). In summary, despite some conflicting studies regarding a positive role of estrogen following TBI, the vast bulk of the data clearly support a neuroprotective role for both estrogen and progesterone.

SEVERITY

Historically, concussion severity has been judged according to 1) the actual nature of the injury (e.g., a sledgehammer blow to the head versus a fall against a wall versus an elbow to the chin; (2) whether consciousness was lost; (3) the duration of LOC; (4) overall scores on measures of consciousness (e.g., the Glasgow Coma Scale); (5) alterations in reflexes; (6) the extent of post-traumatic amnesia; (7) the number of physical and cognitive symptoms; and (8) the posttrauma duration of physical and cognitive symptoms (Esselman & Uomoto, 1995; Gronwall, 1991). The first five of these criteria involve outcomes of the instant, whereas the latter three may involve measurements well after the event.

Issues of functional severity are presented elsewhere in this volume. The discussion here will cover the context of the forces causing concussion and the resulting physiological changes.

Physical Forces

Several authors have commented on the physical forces that are necessary and sufficient to cause head injury in animals or humans, and have suggested that severity of injury and neurocognitive impairment can be estimated by the acceleration–deceleration forces (Barth, Varney, Ruchinskas, & Francis, 1999; Barth et al., 2001). Not surprisingly, the most quantifiable experimentally generated information comes from animal studies. However, because of the very distinct differences between animals and humans in this regard—particularly the ability of small animals to withstand major blows with impunity—the specific values of force, mass, and rotation that are sufficient to cause concussion or worse brain injuries in animals may have little bearing on humans. For example, Unterharnscheidt (1970) reported that a single translational blow of about 315 *g* force for cats and 400 *g* for rabbits was sufficient to cause concussion along with secondary traumatic lesions in deep brain and brainstem structures. The effects of rotational acceleration were studied in squirrel monkeys, where it was reported that values of about 1.5×10^5 rad/sec^2 were sufficient to cause concussion-like effects and secondary traumatic injury (Unterharnscheidt, 1970). Finnie (2001) has provided a detailed review of the strengths and weaknesses of the various animal models.

With respect to the human condition, Naunheim, Standeven, Richter, and Lewis (2000) indicated in their review that a score in excess of 1,500 on the Gadd Severity Index, or above 1,000 on the Head Injury Criterion (HIC), or a peak accelerative force of 200 *g* should be considered thresholds for single impacts likely to "cause a significant brain injury" in humans. These val-

ues were estimated based upon the animal studies and observations of accident outcomes in humans. Moreover, Naunheim et al. (2000) also measured peak accelerative forces in athletic competition by using an accelerometer embedded in helmets worn by soccer, football, and ice hockey players. They recorded no impacts that approached the 200 *g* level, but neither did they observe any events that were correlated with reports of concussion. That limits any possible conclusion other than the obvious one that concussive level forces likely occur with relative (and fortunate) infrequency in these sport contexts. In their attempt to study the concussion risk of the force-mass collisions that occur in soccer heading, Schneider and Zernicke (1988) created an elegant computer simulation model within which the characteristics of the human participant along with the ball factors (acceleration, vector, mass) could be varied. After first calculating typical accelerative forces in players and nonplayers who were participating in a moderate heading drill, they applied the obtained acceleration, mass ratio, and duration values to the model. Their results confirmed the usual finding that rotational forces were much more problematic in concussion risk, and also showed that unsafe values of the HIC (>1,000) and peak accelerative force (>1,800 rad/sec^2) occurred when children were modeled in both translational and rotational acceleration conditions, and for adults in the rotational condition. The mass ratio appeared to be a critical determinant of the attainment of unsafe forces, and Schneider and Zernicke issued a plea for using smaller-mass soccer balls in environments where children might be participating.

Barth et al. (2001) conservatively calculated the deceleration of the brain of a running back in football following a tackle to be about 4.46 *g*. Typical accelerative forces measured by an accelerometer in the padding of a helmet worn by soccer players showed average forces of 49 *g* upon heading a ball traveling at 39 miles per hour (Lewis et al., 2001). Clearly, the range of accelerative forces operating within a sports environment varies considerably, yet it appears to be less than the levels that may cause head injuries in motor vehicle crashes (Gurdjian, 1972a, 1972b).

Acute Effects of Repetitive Blows

Second-impact syndrome (SIS) describes injury-induced vulnerability to further cerebral concussion. Over the past 20 years, there have been a number of reports of sudden collapse and death following seemingly minor concussive incidents. In several of these incidents, it was discovered that the individual had recently suffered another concussion (Cantu & Voy, 1995). Although the original observations of second-impact syndrome occurred in human case-history studies, the fundamental data that support the phenomenon have

arisen in animal studies. In the animal experimental literature we now have reports that two or more concussive blows in close succession have produced significantly greater neurological impairment and resulting neurobehavioral deficits than a simple sum of these singular blows would have predicted (Fu, Smith, Thomas, & Hovda, 1992; Laurer et al., 2001). Moreover, in a study with transgenic mice who expressed a mutation of the human amyloid precursor protein, it was found that repeated but not single concussive blows accelerated the deposition of beta-amyloid, a phenomenon likened to the accumulation of beta-amyloid in human Alzheimer disease sufferers (Uryu et al., 2002). Thus, in addition to the prospect that repeated concussive blows may cause extremely serious acute impairments, we now must entertain the possibility that a history of concussive blows early in life may have morbid effects much later. Such a scenario has been described previously with aging former professional football players (Kutner, Erlanger, Tsai, Jordan, & Relkin, 2000).

As described previously, Hovda and his colleagues have shown that the initial concussion creates a neurometabolic cascade of events in which energy stores are depleted through excitotoxic mechanisms, with accompanying ionic fluxes of great magnitude and neuronal/axonal impairment and injury (Giza & Hovda, 2001; Hovda et al., 1999). In rats, there apparently is at least a 3-day vulnerability to reduced CBF, which could be due to such metabolic dysfunction (Hovda et al., 1999; Doberstein, Hovda, & Becker, 1993). If a second concussive event occurs within this period of metabolic instability and vulnerability, then the brain may be incapable of dealing with the decreased CBF and the hypermetabolic phenomena of the second concussion. In that instance the probability of neuronal mortality increases greatly (Giza & Hovda, 2001). Of great importance, Hovda and colleagues also have extended these findings to humans. They have now documented that glucose hypometabolism characterizes the post-TBI patient, creating potential energy crises when the need for increased energy utilization arises (Bergsneider et al., 2000). Thus, Hovda and others have provided a mechanism that can explain disastrous outcomes of further head injury following an initial concussion.

Cumulative Effects of Repetitive Concussions

From a clinical standpoint, it has been reported previously that a history of concussion represents a significant risk for future concussion (Collins, Lovell, Iverson, Cantu, & Maroon, 2002; Gerberich, Priest, Boen, Straub, & Maxwell, 1983). The mechanism that controls such an increased risk has not been identified. Guskiewicz et al. (2003) suggested that the known mecha-

nisms of impaired glucose metabolism following a single concussive event are likely components of the risk factor of multiple concussions. However, it is not clear from the animal or human data exactly what part of the postconcussion neural cascade may be causative. Geddes, Vowles, Nicoll, and Revesz (1999) found increased neuropathology in the brains of young men (mostly boxers) who had suffered mild chronic head injury. The primary markers were neurofibrillary tangles (though in the absence of beta-amyloid), and the authors speculated that vascular changes might have been pathogenic. Although one may question the linking of boxing outcomes to the sequelae of other sport-related concussions, Rabadi and Jordan (2001) have suggested that sufficient data exist to anticipate the finding of cumulative neurological consequences in soccer, ice hockey, football, and the martial arts, not unlike the results reported for boxers.

Gaetz, Goodman, and Weinberg (2000) studied junior ice hockey players who had suffered one, two, or three concussions at least 6 months earlier. The event-related P3 potential was significantly delayed in latency (but not in amplitude) following stimulation only in players with a history of concussion. The electrophysiological change corresponded to increased self-reports of postconcussion symptoms. Since the P3 measure is generally accepted to represent a cognitive response to stimulation, the increased latency corresponds to a hypothesized disruption in some number of cortical cells or pathways, but not the large number that might be expected to produce a significant decrease in the amplitude of the response.

Subconcussive Blows

A subconcussive event may be defined as an apparent brain insult with insufficient force to cause hallmark symptoms of concussion. The rationale for wrapping subconcussive events into the context of concussion is that impairment from TBI may exist on a continuum of histologically based damage. However, for the very reason that subconcussive events are not as easily identified as are concussions, it is conceptually problematic to make the link to any observed impairment. The major impetus for considering subconcussive outcomes is the fact that such events are common in sports such as soccer and football, as well as in boxing. In 1941, Denny-Brown and Russell observed that "we were surprised to find that even subconcussive blows induced an immediate increase of jugular outflow, whether the carotids were patent or not" (pp. 126–127). They tied this vascular phenomenon to vagoglossopharyngeal stimulation by the subconcussive event and concluded that such vascular phenomena were not a necessary part of concussion (as operationalized by them). The potential that repeated subconcussive blows to the

head might cause equivalent if not greater damage than a single mild concussion was noted by Unterharnscheidt (1970) in his observations of the effects of boxing, and it was summarized later by Cantu and Voy (1995). Much of the controversy regarding the risks of heading in soccer stems from the potential for damage from subconcussive events to accumulate and cause functional or structural impairment (Witol & Webbe, 2003).

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