CHAPTER 1

NEUROPHYSIOLOGY OF CONCUSSION: THEORETICAL PERSPECTIVES

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Abstract: Cerebral concussion is both the most common and most puzzling type of traumatic brain injury (TBI). In this review brief historical data and theories of concussion which have been prominent during the past century are summarized. These are the vascular, reticular, centripetal, pontine cholinergic and convulsive hypotheses. It is concluded that only the convulsive theory is readily compatible with the neurophysiological data and can provide a totally viable explanation for concussion. The chief tenet of the convulsive theory is that since the symptoms of concussion bear a strong resemblance to those of a generalized epileptic seizure, then it is a reasonable assumption that similar pathobiological processes underlie them both. According to the present incarnation of the convulsive theory, the energy imparted to the brain by the sudden mechanical loading of the head may generate turbulent rotatory and other movements of the cerebral hemispheres and so increase the chances of a tissue-deforming collision or impact between the cortex and the boney walls of the skull. In this conception, loss of consciousness is not orchestrated by disruption or interference with the function of the brainstem reticular activating system. Rather, it is due to functional deafferentation of the cortex as a consequence of diffuse mechanically-induced depolarization and synchronized discharge of cortical neurons. A convulsive theory can also explain traumatic amnesia, autonomic disturbances and the miscellaneous collection of symptoms of the post-concussion syndrome more adequately than any of its rivals. In addition, the symptoms of minor concussion (i.e., being stunned, dinged, or dazed) are often strikingly similar to minor epilepsy such as petit mal. The relevance of the convulsive theory to a number of associated problems is also discussed.

Keywords: ANS, autonomic nervous system; ARAS, ascending reticular activating system; BSRF, brainstem reticular formation; DAI, diffuse axonal injury; MRI magnetic resonance imaging; TBI, traumatic brain injury; CBF, cerebral blood flow; CSF, cerebrospinal fluid; GSA, generalized seizure activity, ICP, intracranial pressure.

1. INTRODUCTION

Cerebral concussion is a short a short-lasting functional disturbance of neural function typically induced by a sudden acceleration or deceleration of the head usually without skull fracture (Trotter, 1924; Denny-Brawn & Russell, 1941; Symonds, 1962; Ward, 1966; Walton, 1977; Shelter & Demakas, 1979; Plum & Posner, 1980; Bannister, 1992; Rosenthal, 1993; Label, 1997). Falls, collisions, contact sports such as hockey, football and boxing as well as skiing, horseback riding and bicycle accidents are among the major causes of concussion (Kraus & Nourjahm 1988). Concussion is not only the most common type of traumatic brain injury (TBI), but also one of the most puzzling of neurological disorders. The most obvious aspect of concussion is an abrupt loss of consciousness with the patient dropping motionless to the ground and possibly appearing to be dead. This is usually quite brief, typically lasting just 1–3 min, and is followed by a spontaneous recovery of awareness. Definitions of concussion was almost always qualified by the statement that the loss of consciousness can occur in the absence of any gross damage or injury visible by light microscopy to the brain (Trotter, 1924; Denny-Brawn & Russell, 1941). However, more recent evidence suggests that loss of consciousness is not necessarily accompanied by mild TBI. Neuropathological changes may or may not present following concussion. Therefore, it was assumed that concussion is a disorder of functional rather than structural brain abnormality (Verjaal & Van 'T Hooft, 1975). The quantitative viewpoint of concussion was strongly advocated in a famous paper by Sir Charles Symonds published 40 years ago (Symonds, 1962). In this, Symonds argued that "concussion should not be confined to cases in which there is immediate loss of consciousness with rapid and complete recovery but should include the many cases in which the initial symptoms are the same but with subsequent long-continued disturbance of consciousness, often followed by residual symptoms. Concussion in the above sense depends upon diffuse injury to nerve cells and fibres sustained at the moment of the accident. The effects of this injury may or may not be reversible."

This transient comatose state is also associated with a variety of more specific but less prominent signs and symptoms. Upon the regaining consciousness, headache, nausea, dizziness, vomiting, malaise, restlessness, irritability and confusion may all be commonly experienced. The most significant effect of concussion besides loss of awareness is traumatic amnesia (Russell & Nathan, 1946; Symonds, 1962; Fisher, 1966; Benson & Geschwind, 1967; Yarnell & Lynch, 1979; Russell, 1971). There appears to be an intimate link between amnesia and concussion so much so that if a patient claims no memory loss, it is unlikely that concussion has occurred (Denny-Brawn & Russell, 1941; Verjaal & Van 'T Hooft, 1975). Traumatic

amnesia can be manifested within two common forms. Pre-traumatic or retrograde amnesia refers to loss of memory for events which transpired just prior to the concussion. Post-traumatic or anterograde amnesia applies to loss of memory for events after consciousness has been regained. It is often assumed that the severity of a concussive blow can be measured by the duration of post-traumatic amnesia (Russell, 1971). It has frequently been pointed out that any adequate theory of the pathobiology of concussion must be able to account for not only loss of consciousness but also for its other significant symptoms, specifically the loss of memory (Ommaya & Gennarelli, 1974; Verjaal & Van 'T Hooft, 1975). The traumatic amnesia in both forms is one of the key features on which many theories of concussion are built. Among the most common features of the post-concussion syndrome are: headache, giddiness or vertigo, a tendency to fatigue, irritability, anxiety, aggression, insomnia and depression. These may be associated with problems at work and loss of social skills. In addition, there is a general cognitive impairment involving difficulties in recalling material, problems with concentration, inability to sustain effort and lack of judgment. The essential mystery of concussion does not pertain to an understanding of its biomechanics, nor to why it possesses amnesic properties, nor to the etiology of the post-traumatic syndrome, nor to its relationship to other forms of closed head injury, nor to the significance of any neuropathological changes which may accompany it. Rather, it is the paradox of how such a seemingly profound paralysis of neuronal function can occur so suddenly, last so transiently, and recover so spontaneously. As Symonds (1974) has again pointed out, no demonstrable lesion such as "laceration, edema, hemorrhage, or direct injury to the neurons" could account for such a pattern of loss and recovery of consciousness and cerebral function. The almost instantaneous onset of a concussive state following the blow, its striking reversibility, the seeming absence of any necessary structural change in brain substance plus the inconsistency of any neuropathology which may occur are all compatible with the conception of concussion as fundamentally a physiological disturbance.

2. HISTORICAL BACKGROUND

The term *concussion* is relatively modern, although, having been coined back in the 16th century. According to the *Oxford English Dictionary*, the word concussion is derived from the Latin *concutere*. It refers to a clashing together, an agitation, disturbance or shock of impact. The term concussion therefore conveys the idea that a violent physical shaking of the brain is responsible for the sudden temporary loss of consciousness and/or amnesia. It is, in general, synonymous with the older expression *commotio cerebri* (Ommaya & Gennarelli, 1974; Levin et al., 1982), a term which still can be

found in some contemporary texts. A more recent title is that of traumatic unconsciousness although this may lack the specificity of concussion or *commotio cerebri* (Ommaya & Gennarelli, 1974). More recently, a term such as mild TBI has been fashionable (Kelly, 1999 and Powell and Barber-Ross, 1999). The French military surgeon Ambroise Paré (1510–1590) is sometimes credited with introducing the name concussion but he certainly popularized it when he wrote of the "concussion, *commotio* or shaking of the brain" (Frowein & Firshing, 1990).

Despite its ancient recognition, attempts to understand the pathobiology of concussion are comparatively recent and date back not much further than the Renaissance. Medieval medicine contributed little to this problem with the notable exception of the 13th century Italian surgeon Guido Lanfranchi of Milan (?–1315). Exiled in Paris, Lanfranchi (a.k.a. Lanfrancus or Lafrance) taught that the brain is agitated and jolted by a concussive blow (Muller, 1975). His textbook *Chirurgia Magna* (c. 1295) is often credited with being the first to formally describe the symptoms of concussion (Robinson, 1943; Skinner, 1963; Morton, 1965; Sebastian, 1999). Notwithstanding this claim, the protean Persian physician Rhazes (c. 853–929) considered the nature of concussion in his Baghdad clinic some 400 years before Lanfranchi. He clearly appreciated that concussion could occur independently of any gross pathology or skull fracture (Muller, 1975). Yet a third candidate with a claim to first describing the symptoms of concussion in a systematic manner was another Italian surgeon, Jacopo Berengario da Carpi (1470–1550), a contemporary of Ambroise Paré. He believed that the loss of consciousness following concussion was triggered by small intracerebral hemorrhages (Levin et al., 1982). However, this notion was at odds with the more widely held notion of Paré that concussion is a kind of short-lasting paralysis of cerebral function due to head and brain movement and that any associated fractures, hemorrhages or brain swelling were by-products of the concussion rather than a direct cause of it (Denny-Brown and Russell, 1941; Ommaya et al., 1964; Parkinson, 1982; Muller, 1975; Frowein & Firsching, 1990).

By the end of the 18th century enough information had been amassed on the nature of concussion to allow a now classic definition to be formulated. This was written in 1787 by Benjamin Bell (1749–1806), a neurosurgeon and entrepreneur at the Edinburgh Infirmary (and incidentally grandfather of Sherlock Holmes prototype Joseph Bell). According to Bell, "every affection of the head attended with stupefaction, when it appears as the immediate consequence of external violence, and when no mark or injury is discovered, is in general supposed to proceed from commotion or concussion of the brain, by which 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." This definition has been widely reproduced in the modern

concussion literature (e.g. Foltz & Schmidt, 1956; Ward, 1996; Gronwall & Simpson, 1974; Shetter & Demacas, 1979), indicating that even after 200 years it remains a well-founded description which has stood the test of time (Haymaker and Schiller, 1970). During the 19th century, neurologists were concerned with attempting to reconcile how the seemingly severe paralysis of neural function associated with concussion could occur with no obvious visible damage (Levin et al., 1982). For example, in 1835 J. Gama proposed that "fibers as delicate as those of which the organ of mind is composed are liable to break as a result of violence to the head" (Strich, 1961). This is a quite prescient idea which has a modern echo in the theory that even minor forms of closed head injury may be underlain by some degree of diffuse axonal injury (DAI) caused by widespread tearing or stretching of nerve fibers (e.g. Oppenheimer, 1968; Gennarelli et al., 1982a; Jane et al., 1985). During the first part of the 20th century, there was continuing development of animal models of mechanical brain injury and an associated development of a variety of theories of concussion such as molecular, vascular, mechanical and humoral hypotheses (Denny-Brown & Russell, 1941). There was also an upsurge of interest into the previously rather neglected area of traumatic amnesia and its possible prognostic role in determining the severity of concussion (Russell, 1932; 1935; Cairns, 1942; Muller, 1975, Levin et al., 1982). Still, the modern era in the study of concussion is usually assumed to begin in the early 1940s when a series of seminal papers were published. These included the landmark studies by the New Zealand neurologist Derek Denny-Brown and co-workers at Oxford (Denny-Brown & Russell, 1940; 1941; Williams & Denny-Brown, 1945), the complementary research by the physicist Holbourn, (1943, 1945) and the ingenious cinematography experiments of Pudenz & Shelden (1946). Among the chief concerns of Denny-Brown & Russell (1941) were the biomechanics of concussion. Subjects for their experiments were mostly cats but monkeys and dogs were also employed. Animals were concussed with a pendulum-like device which struck the back of the skull while they were lightly anesthetized, usually with pentobarbital. What was most radically innovative about this technique was that animals were struck by the pendulum hammer while their heads were suspended and therefore free to move. This was at variance with the long-standing method where a concussive blow was often delivered while the animal's head lay immobilized on a hard table surface. The authors reported that when the head was unrestrained, concussion readily ensued. In contrast, when the head was fixed, concussion was difficult, if not impossible, to attain. Denny-Brown and Russell described the type of brain trauma dependent upon a sudden change in the velocity of the head as acceleration (or deceleration) concussion. This was to distinguish it from the second form of concussion which was labeled compression concussion. Compression concussion was thought to arise from a transient increase in ICP due to changes in skull

volume caused by its momentary distortion or depression following a crushing type of impact. Denny-Brown and Russell formally studied compression concussion by sudden injection of a quantity of air into the extradural space creating a large abrupt rise in ICP. This procedure produced a concussive-like state which by and large resembled that of accelerative trauma. Nevertheless, the authors could find only minimal evidence of an increase in ICP during accelerative concussion in their animals, certainly not enough to account for the symptoms of concussion. These findings were interpreted to mean that accelerative and compressive concussion had somewhat different modes of action. Compression concussion was assumed to be associated with a marked elevation in ICP. This conclusion was consistent with the recent study by Scott (1940). In this experiment, concussion had been attributed to a sharp increase in ICP which was able to be recorded immediately after impact to the immobilized head in the dog subjects. In contrast, the necessity to move the head implied that the crucial factors in acceleration/deceleration concussion were the relative momentum and inertial forces set up within the brain and skull. Both forms of concussive injury, however, were believed to ultimately paralyze brainstem function.

Denny-Brown and Russell had emphasized the importance of head movements in the elicitation of concussion. Shortly afterwards Holbourn (1943; 1945) another Oxford investigator, defined more precisely the biomechanics of cerebral damage. Holbourn did not use animals for these experiments. Instead, he constructed physical models consisting of a wax skull filled with colored gelatin which substituted for the substance of the brain. These models were then subjected to different kinds of impact. Holbourn observed that a brain was relatively resistant to compression but more susceptible to deformation. He therefore reasoned that angular acceleration (or deceleration) of the head set up rotational movements within the easily distorted brain generating shear strain injuries most prominently at the surface. Holbourn's experiments appeared to confirm his predictions that rotational motion was necessary to produce cortical lesions and probably concussion. In contrast, linear or translational forces played no major role in the production of shear strains and therefore presumably brain damage following closed head trauma. Thirty years later the basic tenets of Holbourn's theory were more or less confirmed using animals rather than physical models (Ommaya & Gennarelli, 1974). When squirrel monkeys were subjected to rotational acceleration, they suffered a genuine concussion as predicted by Holbourn. In contrast, animals subjected to linear acceleration showed no loss of consciousness although many sustained cortical contusions and subdural hematomas. The physical modeling and theoretical calculations of Holbourn implied a crucial role for rotatory movements within the cranial vault in the elicitation of concussion. The nature and extent of these were dramatically demonstrated soon after by

Pudenz and Shelden (Shelden & Pudenz, 1946) using the monkey as subject. The top half of the skull was removed and replaced with a transparent plastic dome. Following accelerative trauma, the swirling and gliding motion of the brain's surface was then able to be captured using high-speed cine-photography. It was also documented how, upon rotational head movement, the brain lags noticeably behind the skull due to its relative inertia.

At least partially inspired by studies such as those summarized above, there was a virtual exponential growth in the development and employment of animal models of concussion during the second half of the 20th century (Gordon & Ponten, 1976). These have utilized a wide range of both higher and lower mammals including rats, mice, cats, ferrets, pigs, squirrel monkeys, baboons and chimpanzees. A prodigious array of techniques to induce experimental mechanical brain injury has been devised. Following the precedent of Denny-Brown & Russell, most can be fairly easily categorized as inducing either accelerative or compressive concussion. Initially, as Shetter & Demakas (1979) have pointed out, accelerative-impact type of devices were most common but in more recent times a compressive model employing fluid percussion has more become popular. The pay-off from such a concentrated effort has been the ability to measure both behavioral changes and pathobiological events, often immediately after concussion, with increasing precision and sophistication. This has been true not only for minor closed head injury such as concussion, but for studies of TBI in general.

3. THEORIES OF CONCUSSION

3.1. The vascular hypothesis

The vascular hypothesis is the oldest of the formal attempts to explain the nature of concussion. The theory held sway for the best part of a century (Symonds, 1962) and Denny-Brown & Russell (1941) have traced its antecedents in the latter part of the 19th century. The vascular hypothesis comes in a variety of guises and its chief tenet is that the loss of consciousness and other functions following concussion are due to a brief episode of cerebral ischemia or, as sometimes described, cerebral anemia (Trotter, 1924; Denny-Brown & Russell, 1941; Walker et al., 1944; Symonds, 1962, 1974; Verjaal & Von'T Hooft, 1975; Nilsson et al., 1977). What mechanism could trigger this ischemic event is uncertain. It has been variously attributed to vasospasm or vasoparalysis, reflex stimulation, expulsion of the blood from the capillaries and, most commonly, obstruction or arrest of CBF following compression of the brain. Especially with regard to the last of these possible causes, this would most likely be due to a sudden momentary rise in ICP produced by deformation or indentation of the skull

following head impact (Scott, 1940). The principal difficulty with the vascular theory is that it cannot readily cope with the immediate onset of unconsciousness and other symptoms. A more recent rebuttal of the vascular theory arose from Nilsson's study of cerebral energy metabolism in the concussed rat (Nilsson & Ponten, 1977). It would be predicted that if ischemic processes did underlie the pathophysiology of concussion, then there should invariably be evidence of deficient energy production. In fact, Nilsson & Ponten were able to demonstrate that a genuine concussive state could still be maintained in their animals without any marked exhaustion in energy reserves.

3.2. The reticular hypothesis

The reticular theory has been the predominant explanation for the pathophysiology of mild traumatic brain injury for the best part of half a century (e.g. Foltz et al., 1953; Foltz & Shcmidt, 1956; Chason et al., 1958; Ward, 1966; Friede, 1961; Ward. 1966; Brown et al., 1972; Martin, 1974; Walton, 1977; Povlishock et al., 1979; Plum & Posner, 1980; Levin et al., 1982; Smith. 1988; Roppe, 1994; Adams et al., 1997). It is sometimes considered so self-evidently correct that it has almost acquired the status of a dogma. The attraction of the hypothesis is that it appears to provide a mechanism of action which adequately links an apparent brainstem site of action of concussion with the subsequent but quickly reversible loss of consciousness. The major tenet of the reticular theory is that a concussive blow, by means which have never been satisfactorily explained, temporarily paralyses, disturbs or depresses the activity of the polysynaptic pathways within the reticular formation. According to the reticular theory, unconsciousness following concussion would therefore be mediated by much the same processes that produce stupor or coma following a lack of sensory driving of the ascending reticular activation system (ARAS) or electrolytic destruction of the reticular substance. Once the reticular neurons begin to recover, the ARAS becomes operational again. The cortex can then be re-activated and control can be regained over the inhibitory mechanisms of the medial thalamus. A more or less spontaneous return of awareness and responsiveness would then be expected. It should be noted that despite the pervasiveness of the reticular theory as an explanation for concussion, comparatively little worthwhile evidence seems to have been assembled in its favor. Among the most widely cited are neurophysiological studies, especially those of Foltz & Schmidt (1956). However, there is also quite a large amount of neuropathological data which is at least compatible with the reticular theory (Plum & Posner, 1980). For example, following experimental concussion, it has been demonstrated that hemorrhagic lesions, alterations in neuronal structure, axonal degeneration, depletion in cell count

and other cytological and morphological changes may be observed, either in the brainstem generally, or more specifically within the reticular substance.

Apart from somatic damage, there is also evidence that brainstem neurons may undergo at least a limited form of axonal degeneration following concussion. Oppenheimer (1968) examined the brains of patients who had died following head injury. Most of Oppenheimer's subjects had suffered severe head trauma but a minority had only what was described as a clinically trivial concussion and had died of other causes. These subjects therefore provided a rare opportunity to study any neuropathological correlates of simple concussion in humans. Oppenheimer found that even following minor head trauma, microscopic lesions indicative of axonal damage could be discovered scattered throughout the white matter. These commonly took the form of microglial clusters within the brainstem. Oppenheimer also observed that these microglial reactions could be detected specifically within the brainstem and commented that it was from the same location that Foltz and Schmidt (1956) had recorded depressed EP activity in the supposedly concussed monkey.

There is even debate over the more modest claim that the neuropathological data might at least provide evidence of a brainstem site of action for concussion. There is, for instance, danger of a self-fulfilling prophecy when signs of neuronal damage are searched for only within the BSRF (e.g. Brown et al., 1972). Secondly, neuronal disruption within the BSRF might not necessarily indicate a primary brainstem site of action. Finally, there is the puzzling discrepancy between the findings of Jane et al. (1985) discussed above and those of Gennarelli et al. (1982a). Both studies were conducted in the same institution, employed the same non-impact acceleration model of closed head injury and used the monkey as subject. Animals who suffered severe head trauma showed DAI, the extent of which was proportional to the duration of the coma (Gennarelli et al., 1982a). However, in contrast to the findings of Jane et al., in subjects which were simply and briefly concussed, no evidence of DAI could be observed. It is this sort of inconsistency which tends to reinforce the suspicion that brainstem neuropathological changes accompanying concussion may just be a by-product of the mechanical trauma. They may therefore not be directly relevant to the identification of either the site or mechanism of action of concussion.

3.3. The Centripetal Hypothesis

The centripetal theory is an ambitious, ingenious but ultimately flawed attempt to explain the mechanism of action of concussion and to deal with many of its symptoms. Its progenitors were two neurosurgeons, Ommaya & Gennarelli, who outlined their theory in a series of papers published in the

mid 1970s (Ommaya & Gennarelli, 1974, 1975, 1976). The centripetal theory has eclectic origins which include the ruminations of Symonds (1962), the physical modeling and theoretical calculations of Holbourn (1943) as well as the series of studies that Ommaya and co-workers had conducted on primates during the previous decade (Ommaya et al., 1964, 1966, 1968, 1973; Ommaya & Hirsch, 1971; Letcher et al., 1973). In these, an understanding of the principles of the biomechanics of closed head injury had been increasingly refined. One of the most valuable insights arising from these investigations was the demonstration that non-impact (impulse) inertial loading was itself sufficient to induce concussion. This indicated that the contact phenomena associated with the direct impact injury was not crucial to the production of a concussive state even if it was capable of inflicting damage to the skull or brain. Ommaya & Gennarelli also confirmed Holbourn's theory that it was the rotational, rather than translational, component of inertial loading which was solely responsible for concussion. It will be recalled from the discussion of SEPs that angular acceleration of the head resulted in an instantaneous loss of consciousness and abolition of the cortical SEP. In contrast, linear acceleration had little or no effect on either level of arousal or the EP waveform. Judging by Holbourn's analysis plus various mathematical models of the brain's response to acceleration trauma (e.g. Joseph & Crisp, 1971), it is clear that rotational acceleration would exercise its maximum or primary impact at the periphery or surface of the brain. This signified the rather heretical conclusion that the principal site of action of concussion must lie, not deep within the brainstem, but rather just superficially at the cortex. According to Ommaya & Gennarelli's theory, sudden rotational forces set up shearing strains and stresses within the brain immediately upon mechanical loading. These disengage or disconnect nerve fibers in a basically centripetal fashion. When the magnitude of the mechanical loading is comparatively small, such decoupling is functional, reversible and confined to the superficial layers of the brain. As the extent of the accelerative trauma strengthens, the shearing and tensile strains penetrate progressively more deeply into the brain and the disconnections may become more structural and possibly irreversible. The essence of the centripetal theory is summarized in the following quote which is frequently reproduced. Cerebral concussion is conceived 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" (Ommaya & Gennarelli, 1974). It is obvious that such a model of closed head injury views simple transient concussion as differing only in degree from that of more severe head trauma, a conclusion essentially the same as

that of Symonds (1962). More specifically, if the sudden energy imparted to the brain by the inertial forces (i.e. acceleration) is sufficient to decouple only the subcortex or the diencephalon from the cortex, then amnesia and/or confusion may occur but not loss of awareness. Under such conditions, a patient would be best described as being merely stunned or disoriented. Only when the stresses and strains are powerful enough to disconnect the cortex from the much less vulnerable mesencephalon will a genuine loss of consciousness ensue. Disconnection of the brainstem will disrupt the function of the ARAS within the rostral BSRF as well as paralyzing motor performance. Depending upon the severity of the stresses and subsequent disconnection between the cortex, subcortex, diencephalon and mesencephalon will determine whether the outcome is a short or prolonged period of coma, persistent vegetative state (PVS) or death. It can also be deduced from this brief description of the workings of the centripetal theory that it generates a number of quite explicit predictions. Among the most important is that head injury resulting in traumatic unconsciousness will always be accompanied by proportionally greater damage to the cortex and subcortex than to the rostral brainstem. A corollary of this principle is that primary brainstem injury will never exist in the absence of more peripheral damage. Diffuse damage to, or dysfunction in, several locations within the brain may each produce unconsciousness or coma (Plum & Posner, 1980). The centripetal theory conceives concussive forces as primarily targeting activity within the outer layers of the brain. However, in this respect, it is also important to note that the theory does not maintain that any such general impairment with cortical processes is itself responsible for inducing a loss of consciousness. This point has sometimes been misunderstood (e.g. West et al., 1982). Rather, the mechanism of action is still thought to lie within the BSRF, far removed from the primary site of action. Despite appearances to the contrary, the centripetal theory is at heart really only a more complex variation of the reticular theory.

3.4. The Pontine Cholinergic System Hypothesis

The pontine cholinergic system theory was developed during the 1980s by Hayes, Lyeth, Katayama and co-workers at the Medical College of Virginia. Like the centripetal theory, it arose in part because of the perceived inadequacies of the reticular theory. The authors have succinctly captured the difference between the pontine cholinergic and the reticular theories. Both locate the mechanism of action of concussion within the brainstem but for the reticular theory, concussion is associated with depression of an activating system. By comparison, for the pontine cholinergic theory, concussion is associated with an activation of a depressive or inhibitory system (Hayes et al., 1989). During that decade the

authors published a large number of studies in support of the theory. These used both rats and cats as subjects and the standard fluid percussion device to generate concussive brain injury (Sullivan et al., 1976; Dixon et al., 1987). Experiments often involved examining the effects of cholinergic agonists and antagonists on the behavior or electrophysiological function of animals which were either normal or had suffered mechanical brain damage. Relevant EP and EEG recordings arising from this work have been discussed in previous sections. The crux of the theory is that mechanical forces associated with a concussive blow trigger a series of events which activate an inhibitory cholinergic system located within the dorsal pontine tegmentum. This zone is profusely endowed with cholinoceptive and cholinergic cells and pathways. This activation, in turn, suppresses a variety of behavioral responses thought to be indicative of traumatic unconsciousness. As alluded to in the section on the reticular theory, it has long been observed that there is a relationship between both mild and severe head injury with the accumulation of quite large concentrations of ACh in the CSF in which it is not normally present. The ACh appears to progressively leak into the CSF from the damaged neurons but otherwise the exact significance of this release has never been satisfactorily explained (Foltz et al., 1953; Metz, 1971). Increased concentrations of ACh have been reported to occur in the CSF of both experimental animals (Bornstein; 1946; Ruge, 1954; Sachs, 1957; Metz, 1971) as well as patients following craniocerebral injury (Tower & McEachern, 1948, 1949; Sachs, 1957). There also appears to be a positive correlation between the severity of the trauma and the amount of ACh liberated. In addition, it has been claimed that the administration of anticholinergic agents such as atropine may help curtail the duration of coma or unresponsiveness and improve outcome in both experimental animals (Bornstein, 1946; Ruge, 1954) and patients (Ward, 1950; Sachs, 1957).

3.5. The Convulsive Hypothesis

It has long been recognized that the symptoms of concussion appear to overlap those of a generalized epileptic seizure to a remarkable degree (Symonds, 1935; Kooi, 1971; Symonds, 1974; Plum & Posner, 1980). Likewise, the similarity between patients who have been concussed and those who have received electroconvulsive therapy (ECT) has often been noticed (Brown & Brown, 1954; Clare, 1976; Parkinson, 1982), as well as that between animals which have been administered ECS and those which have been experimentally concussed (Brown & Brown, 1954; Belenky & Holaday, 1979; Urca et al., 1981; Hayes et al., 1989). These types of observations have fuelled a lingering but rather inchoate suspicion that the pathophysiological events underlying ictal and post-ictal states may be

related to concussion. This conception that mechanically elicited neuronal excitation and discharge underlies concussive injury is usually referred to as the convulsive theory.

3.5.1. Walker's convulsive theory

The classic formulation of the convulsive theory of concussion was adumbrated in 1944 by Earl Walker and co-workers in the first edition of the *Journal of Neurosurgery* (Walker et al., 1944). More than half a century later, the paper is still widely cited in the head injury literature. Walker extended the insight of Denny-Brown that, contrary to the vascular hypothesis, the pathogenesis of concussion might involve a direct mechanical insult to the neuron. However, unlike Denny-Brown's conception, this process was believed to initially excite rather than temporarily depress cellular function. Walker et al. began their paper by reviewing the work of Duret (1920). Based on experimental animal studies, Duret divided the acute concussive period into a brief initial convulsive (or tetanic) phase, followed by a more long-lasting paralytic or quiescent period. Walker remarks that in clinical concussion, this initial period of excitation has usually been overlooked in favor of the more prominent paralytic phase. Although, Walker et al. do not speculate further on this matter, it is probable that convulsive movements do occur quite commonly in clinical concussion but an untrained witness or casual onlooker fortuitously present at the moment of injury is unlikely to appreciate the significance of any such motor phenomena.

A variety of techniques were utilized to concuss their subjects. These included a hammer blow to the fixed or moveable head, a gunshot to an extracranial part of the head, and a blow delivered directly to the surface of the brain by dropping a weight onto a column of water in contact with the dura mater. Following concussive trauma, all three species of animals used (cats, dogs and monkeys) could display tonic–clonic seizure-like movements. In addition, physiological changes such as increases in blood pressure and bradycardia were attributed to hyperstimulation of the vasomotor centers and vagus excitation, respectively. The presence of acute transient epileptiform activity in the cortical EEG has been shown. Simultaneously, electrical discharges could also be recorded from peripheral nerves and the spinal cord. Based on these and other observations, Walker concluded that the brain's immediate response to a concussive blow was one of hyperexcitability due to widespread neuronal membrane depolarization as a consequence of a shaking up or vibration of the brain. Neuronal exhaustion, inhibition or extinction would account for the subsequent longer and more salient post-ictal period of paralysis, muscle relaxation, behavioral stupor and depressed cortical rhythms. According to Walker's convulsive

theory, the behavioral, physiological and electrical correlates of concussion arise as a consequence of this brief but intense generalized neuronal firing. Concussion is therefore conceived as a kind of epileptic seizure and the mechanisms responsible for the development of its symptoms must be basically the same as those for a spontaneous seizure or one which is generated artificially by chemical, electrical or other means.

If the pathophysiology of concussion primarily involves mechanically-induced convulsive activity, then the question arises as to what is the sequence of events which leads to sudden massive breakdown of the cell membrane potential. Drawing upon the early studies of Gurdjian (Gurdjian & Webster, 1945) as well as those of Scott (1940), Walker et al. demonstrated that the concussive blow creates a zone of increased ICP at the point of impact. This sets in motion vigorous high frequency pressure waves which are transmitted throughout the brain. Such mechanical stresses deform and thereby depolarize neural tissue. Walker et al. cite the findings of Krems et al. (1942) on nerve concussion in support of this contention. In this it was demonstrated that mechanical stimulation of the frog sciatic nerve tissue produced temporary excitation. Walker appeared to believe that linear acceleration was instrumental in generating the pressure waves within the brain. The recent discoveries of Holbourn (1943) on the role of rotational acceleration in producing shearing forces operating principally at the surface of the brain are acknowledged. Nonetheless, the authors remain skeptical of their value when dealing with animals possessing comparatively small heads and brains. Still, it is conceded that either angular or translational acceleration could be responsible for creating ICP waves which ultimately produce a state of traumatic excitation. Fifty years later, in a commemorative article, Walker revisited the convulsive theory and the problem of the physiology of concussion, in general (Walker, 1994). Judging by this paper, he appeared to have lost confidence in the convulsive hypothesis as a credible explanation for concussion during the intervening years. In particular, he is cognizant of the fact that at the time of publication in 1944, it was still some years before Moruzzi, Magoun, Lindsley and others first established the role of the BSRF/ARAS in the control of wakefulness and responsiveness.

3.5.2. Post-Traumatic Loss of Consciousness

Sudden temporary loss of awareness is the most characteristic and enigmatic symptom of concussion. According to Plum & Posner (1980), the maintenance of consciousness is dependent upon a complex interaction between brainstem, thalamus, hypothalamus and cortical activity. It follows, therefore, that a comatose state should ensue if activity within the BSRF is sufficiently disturbed or deranged even if cortical function remains intact.

Conversely, loss of consciousness will also occur following diffuse bilateral impairment of cortical activity even if BSRF function is preserved. Plum and Posner cite a number of studies in support of this latter contention, most notably the work of Ingvar et al. (1978) on the so-called apallic syndrome. The apallic syndrome is somewhat akin to the PVS and consists of subjects who have sustained severe generalized cortical damage often with near complete destruction of telencephalic neurons. Such patients remain deeply comatose even though the evidence suggests that brainstem function, in general, and reticular function, in particular, is at least grossly normal.

Exactly how GSA does induce a state of insensibility is uncertain (Bannister, 1992). Nevertheless, if the correctness of the convulsive theory is accepted, then it is reasonable to assume that the same type of pathophysiological processes which are responsible for the loss of consciousness of an epileptic attack are similarly involved in the loss of consciousness after a concussive injury. At least two theories have been proffered to explain how a generalized epileptic seizure such as grand mal will produce a brief loss of consciousness and responsiveness. Both are related to one or other of the opposing views on the nature of seizure generalization summarized previously. According to the centrencephalon theory, loss of consciousness will ensue when abnormal electrical discharges either invade or arise intrinsically within the pathways and nuclei of the brainstem and thalamic ARAS. This temporarily inactivates ARAS function preventing it from performing its normal role in the maintenance of wakefulness or control of level of arousal. This conception of the pathophysiology of unconsciousness is not much different from that of the reticular theory of concussion. Both involve a disabling of the ARAS. In one instance via a depression of its activity and in the other by an abnormal excitation. In contrast, the cortico-cortical and cortico-reticular theories point to a quite different site and mode of action to explain an acute ictal loss of consciousness. In this case, hypersynchronous cortical epileptiform activity totally blocks reception of sensory signals thereby functionally deafferentating the cortex and rendering the brain insensible and unresponsive. In this arrangement, interference with the brainstem and diencephalic reticular systems does not seem to play a major role in the induction of unconsciousness during a state of GSA (Gloor, 1978). This conception is consistent with the principle outlined at the beginning of this section that a loss of consciousness does not necessarily involve interference with the arousal mechanisms located within the BSRF.

The neurophysiological events described above explain how convulsive activity following a concussive blow could precipitate an acute loss of consciousness. Yet, to reiterate the point made originally by Walker et al. (1944), an acute concussive episode is actually biphasic, consisting of an initial (or ictal) period followed by a long-lasting depressive one. This would be apparent at both behavioral and neuronal levels. Therefore, the

duration of the lack of awareness, insensibility, loss of responsiveness and behavioral suppression which are collectively labeled as unconsciousness (Gloor, 1978) is most appropriately considered the sum of both the ictal and immediate post-ictal phases. The processes underlying the more familiar inhibitory phase of the concussive episode presumably reflect those involved in the cessation of the convulsive activity. Exactly how these operate in any kind of GSA still remains to be determined (Pincus & Tucker, 1985; Engel, 1989).

3.5.3. Traumatic Amnesia

Apart from loss of consciousness, the most distinctive feature of clinical concussion is the occurrence of traumatic amnesia (Fisher, 1966; Russell, 1971). Traumatic amnesia may be used to describe an assortment of memory deficits including retrograde amnesia, anterograde amnesia plus more non-specific disorientation and confusion (Schacter & Crovitz, 1977). Accurately determining the degree of memory impairment following any kind of closed head injury is fraught with methodological problems. Nonetheless, a few general principles have been adduced which are widely accepted. One of these is that the period of retrograde amnesia may progressively shrink during the post-traumatic recovery. Eventually, this may last for only a few seconds (Russell, 1935). Secondly, the length of the anterograde amnesia has often been found to be a generally accurate guide to the severity of the head trauma (Russell & Nathan, 1946; Smith, 1961). This period should not be confused with that of post-traumatic unconsciousness.

As discussed in the earlier section on the similarity between epileptic and concussive symptoms, an epileptic seizure will interfere with the retrograde and anterograde components of learning in much the same fashion as a concussive blow (Holmes & Matthews, 1971; Walton, 1977). Similar memory disorders occur in patients undergoing ECT (Abrams, 1997) and in experimental animals administered ECS (Duncan, 1949). The rule appears to be that if a concussive blow is delivered or GSA is induced in close temporal contiguity to a particular event, then the memory of that event is lost, disrupted or otherwise interfered with. Such studies have provided sustenance to the so-called consolidation theory of memory (Glickman, 1961). The consolidation hypothesis argues that memory is initially encoded in a short-term labile active state and is therefore especially vulnerable to erasure by a disturbing or damaging event such as GSA or a blow to the head. A common conception of this initial process of memory formation is that it is underlain by preservative electrical activity in reverberating neuronal circuits (Hebb, 1949). Eventually, the fragile memory trace evolves or is transformed into a long-term stable passive state which is largely immune to disruption. An amnestic agent would therefore

seem to impair learning or memory by blocking the formation or storage of a more solid permanent memory trace.

3.5.4. Post-Traumatic Autonomic Disturbances

Apart from the major symptoms of loss of memory and consciousness, concussion is also associated with a host of more minor autonomic disturbances (Verjaal & Van 'T Hooft, 1975). These have been summarized elsewhere in the present article and expressly involve alterations in cardiovascular and respiratory function, corneal and pupillary areflexia and gastrointestinal distress. No one autonomic symptom is necessarily present following a concussive insult but at least some of them invariably occur. It has also been pointed out earlier that very similar alterations in autonomic function may accompany a spontaneous epileptic seizure. A convulsive theory can therefore readily deal with the autonomic symptoms of concussion unlike some competing theories which often tend to overlook such phenomena. It can also be assumed that the pathophysiological processes responsible for the tampering with autonomic activity are largely the same for both concussion and epilepsy. These must primarily involve the direct activation of the various systems in the brain which are in overall charge of the autonomic nervous system (ANS) (Everett, 1972) and would particularly include relevant nuclei within the BSRF and the hypothalamus. Excitation of these centers would be mediated by abnormal electrical discharges sweeping down from the cortex. These excitatory bursts would presumably be transmitted in the same or similar cortico-fugal pathways as those which impinge on and energize the motor portions of the BSRF in order to produce convulsant movements. The autonomic nuclei of the brainstem and hypothalamus are thought to wield the same sort of executive tonic control over the ANS as the descending components of the BSRF exert over motor performance (Powley, 1999). Hyperstimulation of these autonomic nuclei will result in widespread activation of both the sympathetic and parasympathetic components of the ANS. Since the operation of these two subdivisions is generally antagonistic, their overall interaction or balance would most likely determine the degree of disturbance of autonomic function. Taken in association with the force of the blow, this most probably accounts for the variability and inconstancy of autonomic symptoms which may occur during a concussive episode (Ommaya et al., 1973; Verjaal & Van 'T;Hooft, 1975; Duckrow et al., 1981; Gennarelli et al., 1982b). Further, the biphasic nature of the convulsive process means that interference with autonomic responses during the initial excitatory period is likely to be different from that during the later inhibitory or paralytic stage. This could also account for some of the discrepancies in reports of changes

in autonomic function following concussion. This is especially so with regard to cardiovascular activity (Shima & Marmarou, 1991).

4. MINOR CONCUSSION: DAZED, DINGED, OR STUNNED

Many patients suffer a mild concussive blow often as a result of a contact sports injury. This is usually described as being stunned, dazed or dinged and is characterized by alterations in mental status or very brief impairment in awareness, rather than a true lapse of consciousness (Cantu, 1992; Kelly, 1999). In their original paper, Walker et al. (1944) reasoned that, whereas concussion was analogous to a grand mal-type of seizure, minor concussion might be equated to a milder petit mal attack. Petit mal is generalized epilepsy of childhood (Marsden & Reynold, 1982; Mirsky et al., 1986; Engel, 1989; Goldensohn et al., 1989; Nashef, 1996). It is characterized electrically by bilateral synchronized three/s spike and wave discharges in the EEG and clinically by a brief period of unresponsiveness or absence in which clouding of consciousness seldom lasts for more than a few seconds. Typically, muscle tone is not lost during this period and victims do not fall to the ground although they may abruptly cease their current activity and sway, stumble or stagger about. Once the attack is terminated, the patient regains awareness almost immediately but remembers nothing of events during the seizure. Expressly comparing a minor concussive episode with a petit mal attack must be done charily. It might be more advisable to follow the example of Symonds (1974) who made the more modest claim of a marked similarity between very mild TBI and minor epilepsy. Nonetheless, it is clear from the symptoms of a petit mal fit outlined above just how closely they resemble a state of being momentarily stunned or dazed following a head blow. This is exemplified by the well-documented instance of the football player who has been dinged or dazed following a subconcussive injury (Yarnell & Lynch, 1973). In the immediate post-traumatic period he is likely to wander around the field, confused, disoriented and amnesic with a glazed-over look (Yarnell & Lynch, 1970; Symonds, 1974; Kelly et al., 1991; Cantu, 1992).

A traumatically-induced minor generalized seizure therefore seems able to account for almost all the phenomena associated with the very common occurrence of a sub-concussive type of closed head injury. In this respect, the convulsive theory can cope with the distinction between full-blown concussion and being merely stunned rather more successfully than some of its competitors. For instance, it will be recalled the conceptual difficulties that the centripetal theory appeared to encounter when dealing with this problem. The tenets of the centripetal theory seemed to imply that a standard concussive insult was restricted to producing just a dazed state of

confusion, disorientation and amnesia. Not until a near fatal blow was delivered could a genuine concussive state with traumatic unconsciousness be created. This kind of discrepancy does not arise with the convulsive theory because it allows for accelerative trauma to produce states of GSA of graded intensity and duration depending upon the severity of the concussive impact. In the case of minor concussion, it would seem that the seizure activity generated by the traumatic force is not sufficiently robust to recruit all the cortical, subcortical and brainstem circuits involved in a full-fledged concussive episode. In many respects, the experimental findings summarized above represent a crucial test of the convulsive theory of concussion. If there had been any substantial disparity between the effects of ECS and those of concussion on the SEP, this may well have dealt the convulsive theory a mortal blow. It is also of interest that quite similar abnormalities occur to the cortical EP following both spontaneous and experimental petit mal seizures (e.g. Mirsky et al., 1986). Notably, the waveform is typically not as severely suppressed as with a grand mal seizure.

CONCLUSIONS

All the five theories of concussion discussed in the present review have been current at times during the past century. They by no means represent an exhaustive list nor should they be considered mutually exclusive. As outlined, the various explanations often overlap one another to a greater or lesser extent. All five offer potentially valuable insights into the pathogenesis of concussion. All or most can supply a reasonable explanation for at least some of the elements of concussion. Nevertheless, it is the contention of this chapter that only the convulsive theory can provide a totally satisfactory account of all the signs, symptoms and other manifestations of concussive injury. If this is a valid conclusion, then it is a matter of interest as to why the convulsive theory has not been more widely accepted or more highly regarded. One of the most significant advantages of a convulsive theory is that any such explanation which is dependent upon the immediate induction of GSA can thereby readily provide an understanding of the most challenging and distinctive features of concussion. These concern the mode of action by which a concussive insult can produce a sudden loss of consciousness and responsiveness, the transient nature of this state and the quite rapid restoration of function. In addition, the convulsant theory can easily account for both traumatic memory loss and the disturbances in the operation of the autonomic system. It can also provide a plausible explanation for the subconcussive state where the victim is stunned rather than genuinely knocked out. In all these respects, the convulsive theory clearly demonstrates its superiority to the more convoluted and less

satisfactory accounts offered by the vascular, reticular, centripetal, pontine cholinergic and other theories of concussion. The current interpretation of the convulsive theory proposes that a concussive insult most likely creates a state of unconsciousness by functional deafferentation of the cortex. Traumatically-induced epileptiform activity is presumed to erect a temporarily insurmountable barrier to the inflow of afferent signals. Bereft of normal sensory stimulation, insensibility immediately ensues. This implies that the processes responsible for loss of awareness during states of sleep or general anesthesia are somewhat different from those mediating short-lasting traumatic coma. Nonetheless, the convulsive theory still envisages a major contribution from reticular mechanisms in other aspects of the pathobiology of concussion. In particular, autonomic, postural and motor disturbances are all presumed to be mediated via an initial excitation and then inhibition of BSRF activity.

A convulsive theory can account for the etiology of the group of personality, affective and other behavioral disorders collectively labeled the post-concussion syndrome, although the extent to which individual symptoms may be organic or psychogenic in origin still remains unresolved (Lishman, 1988; Label, 1977). It may also help to explain some of the cognitive deficits which are reported to occur during this period. A frequently cited example is the post-concussive slowing in information processing as measured by the PASAT (Gronwall & Sampson, 1974; Gronwall & Wrightson, 1974). An increase in anxiety is a common feature of the interseizure period in epileptic patients (Engel, 1989). The cause of this is uncertain although it could well be due to a perceived loss of concentration or lack of attention. As would be predicted by the convulsive theory, anxiety is also a prominent symptom of the post-concussion syndrome. Any upsurge in anxiety level might be expected to have a deleterious effect on the performance of a stressful test. In this respect, a serial addition task such as the one used by Gronwall and co-workers is notorious for its nerve-racking qualities. For instance, Hugenholtz et al. (1988) report a near mutiny among their concussed and control subjects when they were faced with the prospect of having it administered. A concussed patient's performance on the PASAT and similar tests might therefore reflect not so much a direct impairment of cognitive function but rather the abnormal level of anxiety and associated apprehension, fretfulness, irritability and agitation which may linger for sometime after the experience of a generalized seizure. Finally, it will be recalled that the term concussion was classically defined as a violent shaking, jolting, jarring or vibration. As Skinner (1961) pointed out, the word was at first applied to phenomena such as thunder or an earthquake. Thunder is, of course, produced by an abnormal electrical discharge while convulsive movements are often colloquially likened to an earthquake occurring in the body. Indeed, a seismogram can even superficially resemble epileptiform activity

recorded during the tonic phase of a generalized seizure. Perhaps using the term concussion to describe a brief traumatic loss of consciousness may have been an even more felicitous choice than those who initially adapted its usage could have realized.

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Acknowledgements

An earlier full version of this chapter was published as "Neurophysiology of Cerebral Concussion" in *Progress in Neurobiology, 67* (2002), 281-344. Included in this volume with permission from the Elsevier.