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The neurophysiology of concussion

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Abstract

Cerebral concussion is both the most common and most puzzling type of traumatic brain injury (TBI). It is normally produced by acceleration (or deceleration) of the head and is characterized by a sudden brief impairment of consciousness, paralysis of reflex activity and loss of memory. It has long been acknowledged that one of the most worthwhile techniques for studying the acute pathophysiology of concussion is by the recording of neurophysiological activity such as the electroencephalogram (EEG) and sensory evoked potentials (EPs) from experimental animals. In the first parts of this review, the majority of such studies conducted during the past half century are critically reviewed. When potential methodological flaws and limitations such as anesthetic protocols, infliction of multiple blows and delay in onset of recordings were taken into account, two general principles could be adduced. First, the immediate post-concussive EEG was excitatory or epileptiform in nature. Second, the cortical EP waveform was totally lost during this period. In the second parts of this review, five theories of concussion which have been prominent during the past century are summarized and supportive evidence assessed. 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. Further, it is demonstrated that EPs and EEGs recorded acutely following concussive trauma are indeed the same or similar to those obtained following the induction of a state of generalized seizure activity (GSA). 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 (a.k.a. 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. These include the relationship between concussion and more serious types of closed head injury, the utility of animal models of severe brain trauma, the etiology of the cognitive deficits which may linger long after a concussive injury, the use of concussive (captive bolt) techniques to stun farm animals prior to slaughter and the question of why some animals (such as the woodpecker) can tolerate massive accelerative forces without being knocked out.

Abbreviations: ACh, acetylcholine; AEP, auditory evoked potential; ANS, autonomic nervous system; ARAS, ascending reticular activating system; BAEP, brainstem auditory evoked potential; BSRF, brainstem reticular formation; CBF, cerebral blood flow; CSF, cerebrospinal fluid; DAI, diffuse axonal injury; DTPS, diffuse thalamic projection system; EAA, excitatory amino acid; ECS, electroconvulsive shock; ECT, electroconvulsive therapy; EEG, electroencephalogram; EP, evoked potential; FVEP, flash visual evoked potential; GSA, generalized seizure activity; HRP, horseradish peroxidase; ICP, intracranial pressure; MRI, magnetic resonance imaging; PASAT, paced auditory serial addition task; PDS, paroxysmal depolarization shift; PVS, persistent vegetative state; REM, rapid eye movement; SEP, somatosensory evoked potential; TBI, traumatic brain injury; TTX, tetrodotoxin

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Contents

1. Introduction

Cerebral concussion is a short-lasting disturbance of neural function typically induced by a sudden acceleration or deceleration of the head usually without skull fracture (Trotter, 1924; Denny-Brown and Russell, 1941; Symonds, 1962; Ward, 1966; Walton, 1977; Shetter and Demakas, 1979; Plum and Posner, 1980; Bannister, 1992; Rosenthal, 1993; Label, 1997). Falls, collisions, physical assaults, road traffic accidents, contact sports such as hockey, football and boxing as well as skiing, horseback riding and bicycle accidents are among the chief causes of concussion (Kraus and Nourjah, 1988). Concussion is not only the most common and familiar type of traumatic brain injury (TBI), but also one of the most puzzling of neurological disorders. The mystery lies not in the diagnosis of the condition, about which there is little dispute, but rather in the nature of its pathophysiology. The most dramatic 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 are 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-Brown and Russell, 1941; Friede, 1961; Ward, 1966; Nilsson et al., 1977; Shetter and Demakas, 1979; Plum and Posner, 1980; Ropper, 1994). While neuropathological changes may frequently occur, they are neither consistently present nor necessarily associated with the induction of concussion. This implies that concussion is a disorder of function rather than structure (Verjaal and Van 'T Hooft, 1975). This transient comatose state is also associated with a variety of more specific but less prominent signs and symptoms, not all of which may be invariably present. Judging by clinical observations as well as experimental animal studies, these include respiratory arrest or apnea, abolition of various reflex functions including corneal, pupillary and withdrawal responses, relatively prompt flaccidity of the musculature with the patient collapsing into a heap, ephemeral convulsive spasms, irregularities of heart rate including both bradycardia and tachycardia, alterations in cerebral blood flow (CBF) and fluctuations in blood pressure. Upon regaining consciousness, headache, nausea, dizziness, vomiting, malaise, restlessness, irritability and confusion may all be commonly experienced.

Notwithstanding the symptoms outlined above, the most significant effect of concussion besides loss of awareness is traumatic amnesia (Russell and Nathan, 1946; Symonds, 1962; Fisher, 1966; Benson and Geschwind, 1967; Yarnell and Lynch, 1970; 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-Brown and Russell, 1941; Verjaal and Van 'T Hooft, 1975). Traumatic amnesia can be split into two components. 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 multifarious symptoms, especially the loss of memory (Ommaya and Gennarelli, 1974; Verjaal and Van 'T Hooft, 1975). The failure to cope with traumatic amnesia is one of the rocks on which many theories of concussion seem to founder.

One conspicuous feature of concussion is the number of symptoms which may linger long after the head injury has occurred and its acute effects resolved. This potpourri of residual symptoms has been exhaustively catalogued and investigated and is usually described as the post-concussion or post-traumatic syndrome (Strauss and Savitsky, 1934; Taylor, 1967; Kay et al., 1971; Merskey and Woodforde, 1972; Merritt, 1973; Martin, 1974; Symonds, 1974; Rutherford et al., 1977; Walton, 1977; Plum and Posner, 1980; Wrightson and Gronwall, 1981; McMillan and Glucksman, 1987; Hugenholtz et al., 1988; Lishman, 1988; Lowdon et al., 1989; Leininger et al., 1990; Montgomery et al., 1991; Barth et al., 1996; Rizzo and Tranel, 1996). 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 a deterioration in work performance and a 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.

Although ostensibly a simple straightforward form of head injury, the study of concussion is distinguished by many unresolved issues. Some of these are summarized further. The sudden mechanical loading of the head associated with the concussive impact may cause temporary depression of the skull, movement of the head about the axis of the neck, abrupt displacement and rotational movements of the brain within the skull and generation of intracranial pressure (ICP) gradients. Such biomechanical events set up by the concussive blow may ultimately result in stretching, tearing, compression, or deformation injuries to the neural tissue. Disentangling which one, or combination of these factors is ultimately responsible for initiating a state of concussion has proven an arduous task.

A second problem concerns the relationship between transient concussion and more severe kinds of closed head injury in which the period of coma is prolonged. In other words, does concussion have a relatively unique pathogenesis or does it just differ quantitatively from more severe types of head trauma? (Plum and Posner, 1980). If it is the latter, this would suggest that concussion shares the same basic structural or functional injury as more severe brain injury

but differs with respect to the degree of damage and potential for recovery. The quantitative viewpoint 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." Although this viewpoint has been very influential (e.g. Ommaya and Gennarelli, 1974), there is still no consensus on the quantitative versus qualitative dispute (Plum and Posner, 1980; McIntosh et al., 1996).

As described above, concussion is classically defined as occurring without overt morphological damage. Be that as it may, numerous experimental animal studies (and even some clinical data) have documented how histopathological changes in the brain of varying severity and permanence may often accompany concussion. Many of these have been summarized by Nilsson et al. (1977) and Shetter and Demakas (1979) and more recently by Dixon and Hayes (1995) and Povlishock (1995). They quote a multitude of examples where post-concussive examination of the brain has revealed evidence of microscopic and hemorrhagic lesions, neuronal loss and chromatolysis, as well as axonal damage. It is still unclear what, if any, role such organic injury plays in the pathogenesis of concussion. Some have been thought to represent the actual substrate of concussion. Alternately, they may be just a form of neuropathological epiphenomena. At most, these may provide an insight into its site of action. At least, they may be merely an artifact of the particular type of head injury device used (Shetter and Demakas, 1979).

Another enduring controversy concerns the status of the post-concussion syndrome. The persistence of those symptoms after even a mild head injury has led to the suspicion that their origin may be psychogenic rather than organic. Further, such a cluster of symptoms could be exacerbated by the possibility of malingering, neurosis or compensation claims. Nevertheless, careful neuropsychological testing has added weight to the belief that the post-concussion syndrome largely does reflect some kind of residual organic damage. Among the innovative research in this area was that of Gronwall and Wrightson (1974, 1975). They used the paced auditory serial addition task (PASAT) to demonstrate that rate of information processing was slowed in patients who had sustained a concussion. Subsequent recovery in performance tended to correlate with the resolution of post-traumatic symptoms. Unfortunately, the neurogenesis of this sort of deficit in cognitive function and its related psychosocial symptoms still remains to be elucidated (Label, 1997).

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. If this is so, then one of the most appropriate means to gain access to the acute pathophysiological processes would be by the recording of neurophysiological activity such as the electroencephalogram (EEG) and sensory evoked potentials (EPs) following concussion in experimental animals. Both of these are non-invasive measures of cerebral activity and so should be quite readily obtained during a concussive episode. It is a principal purpose of the present article to review the many studies which have attempted to measure the effects of experimental concussion on both the EEG and sensory EPs.

2. Historical background

The origin of the concept of cerebral concussion is shrouded in confusion. The term itself is comparatively modern, having been coined 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. It is, in general, synonymous with the older expression commotio cerebri (Ommaya and Gennarelli, 1975; Levin et al., 1982), a usage which still survives in some contemporary texts (e.g. Verjaal and Van 'T Hooft, 1975). A more recent title is that of traumatic unconsciousness although this may lack the specificity of concussion or commotio cerebri (Ommaya and Gennarelli, 1974). More recently, a term such as mild TBI has been fashionable (Kelly, 1999; Powell and Barber-Foss, 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" (Denny-Brown and Russell, 1941; Verjaal and Van 'T Hooft, 1975; Frowein and Firsching, 1990).

Judging by ancient medical tracts, myths, legends, Biblical texts, plays and poems, it appears that concussion

has been recognized as a distinctive form of head injury since antiquity (McHenry, 1969; Verjaal and Van 'T Hooft, 1975; Parkinson, 1977). For instance, the *Old Testament* recounts how David slew Goliath by initially knocking him unconscious with a rock flung from his sling shot. Ancient physicians clearly understood something of the nature of concussion. One of the precepts in Hippocrates' *Aphorisms* (c. 415 B.C.) is usually translated something like "shaking or concussion of the brain produced by any cause inevitably leaves the patient with an instantaneous loss of voice (i.e. unconscious)" (Verjaal and Van 'T Hooft, 1975; Lloyd, 1978). This is Aphorism no. 58 from Section 7. About the time the *Aphorisms* were being formulated, Aristophanes' satire on Socratic philosophy *The Clouds* was first performed in Athens (423 B.C.) Towards the end of the play, Amynias the money lender appears in a distressed state having just been thrown from his chariot and displaying many of the acute post-concussion symptoms. Some modern translations of *The Clouds* specifically describe Amynias as having suffered a concussion of the brain (e.g. Easterling and Easterling, 1961).

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, 1961; 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 and Firsching, 1990).

More than a century later in 1715, another French surgeon Jean-Louis Petit (1674–1750) provided a further insight by distinguishing between the immediate loss of sensibility due to concussion and a more slowly deteriorating level of consciousness due to brain compression by hemorrhage (Ommaya et al., 1964; Haymaker and Schiller, 1970; Muller, 1975). Petit described concussion as follows: "A fall or a violent blow on the head may cause various degrees of shaking of the brain. This we call commotio" (Verjaal and Van 'T Hooft, 1975). This concussive state was presumed to be generated by the shock waves set up by the head blow being transmitted more or less directly from the skull to the neural tissue (Levin et al., 1982). Also in the early part of the 18th century, Alexis Littré (1658–c. 1727) performed a famous post-mortem which provided telling evidence that concussion may occur without obvious anatomical damage to the brain. The patient had been knocked unconscious after hitting his head against a wall and died soon after (Ommaya et al., 1964; Muller, 1975). Littré could detect no cerebral injury which was consistent with Paré's contention that the symptoms of concussion reflected a functional disturbance rather than a structural deficit involving contusion, hemorrhage or laceration.

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 and Schmidt, 1956; Ward, 1966; Gronwall and Sampson, 1974; Shetter and Demakas, 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).

Following in the footsteps of Paré, another French army surgeon Guillaume Dupuytren (1777–1835) described the symptoms of concussion in detail (Muller, 1975; Frowein and Firsching, 1990). The German neurologists Victor Von Bruns (1811–1883) and Ernst Von Bergmann (1836–1907)

emphasized the transient and reversible nature of the condition as well as the occurrence of autonomic symptoms such as headache, nausea and dizziness (Muller, 1975; Frowein and Firsching, 1990). In the latter part of the 19th century, there was also the beginning of an experimental approach with the development of different animal models. Among the more notable were the behavioral and physiological studies of L. Witkowski in the 1870s using the frog as subject (Povlishock, 1995) and the early neuropathological experiments of H. Schmaus on post-concussive degeneration of nerve fibers in the 1890s (Haymaker and Schiller, 1970).

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 and 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 and Russell, 1940, 1941; Williams and Denny-Brown, 1941; Denny-Brown, 1945), the complementary research by the physicist Holbourn (1943, 1945) and the ingenious cinematography experiments of Pudenz and Shelden (1946).

Among the chief concerns of Denny-Brown and 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.

Although the investigations by Denny-Brown and Russell are rightly considered one of the pioneering studies in the history of experimental concussion, the data presented contain a number of problems of interpretation. Foremost is the criteria that had to be used for concussion. As their subjects were anesthetized, level of consciousness could not be directly assessed (Symonds, 1962). Instead, it was necessary to rely upon changes in reflex activity and measurement of systemic physiological responses. The most reliable indices being loss of corneal and pinna reflexes, alterations in blood pressure and pulse rate, and respiratory disturbances. In addition, Denny-Brown and Russell accounted for the pathogenesis of concussion as being due to direct generalized reversible paralysis of neuronal function. In retrospect, this seems more adequate as a description than an explanation (Nilsson et al., 1977). Despite its limitations and flaws, Denny-Brown and Russell's paper has been immensely influential. It furnished the theoretical and experimental framework for the development of subsequent generations of mechanical head injury devices (Anderson and Lighthall, 1995; Dixon and Hayes, 1995; Povlishock, 1995). In addition, the authors provided an explanation for why otherwise traumatic head injuries such as crushing or missile wounds did not usually result in immediate lose of awareness. If the accelerative trauma does not impart sufficient energy to the head and brain, unconsciousness will not follow.

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 and 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. These matters will be discussed in greater detail in later sections.

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 et al., 1944; Pudenz and Shelden, 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 and 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 and Russell, most can be fairly easily categorized as inducing either accelerative or compressive concussion. Initially, as Shetter and 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 become popular for reasons which will be outlined elsewhere (Section 3.1). 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. The biomechanics of concussion

Any attempt to quantify the biomechanics of even a comparatively simple accelerative-type of head injury is still a formidably difficult task. Numerous factors or considerations need to be taken into account whether dealing with clinical concussion or experimental animal models. These could include: (1) skull shape, size and geometry; (2) density and mass of neural tissue; (3) thickness of scalp and skull; (4) extent, nature and direction of the concussive blow; (5) head–body relationships; and (6) mobility of the head and neck (Shetter and Demakas, 1979; Gennarelli et al., 1982b; Rizzo and Tranel, 1996). This degree of complexity has led some (e.g. Shetter and Demakas, 1979) to question whether a comprehensive understanding of the physical dynamics of concussion can ever be achieved. This problem is not the concern of the present preview. Useful discussions of these matters are available elsewhere (Goldsmith, 1970; Gurdjian, 1972; Ommaya and Gennarelli, 1974; Ripperger, 1975; Unterharnscheidt, 1975; Nilsson et al., 1977; Shetter and Demakas, 1979; Parkinson, 1982; Stalhammar, 1990; McIntosh et al., 1996). Nonetheless, some of the basic principles governing the biomechanics of concussion, which are of particular relevance to the questions raised in this article, are outlined further.

Irrespective of the diverse methods which can be used to deliver a concussive injury, all have at least one feature in common. They all involve the near instant transfer of kinetic energy. This will require either an absorption (acceleration) or release (deceleration) of kinetic energy by the head and brain. According to Newton's law, force is the product of mass and acceleration. However, when dealing specifically with acceleration/deceleration trauma, there can be no ready trade-off between these two components of the mechanical force applied to the head. For instance, a slow sustained crushing impact will injure and damage the skull and brain but will not induce a concussion. Kinetic energy must be transferred and expended rapidly. Conversely, a projectile of small mass such as a high velocity bullet may penetrate skull and brain but also will not induce concussion (Gurdjian et al., 1954). In this instance, the mass of the bullet is too small to impart the necessary kinetic energy to the head. The example of the speeding bullet illustrates an important point regarding the biomechanics of concussion. This is that sufficient kinetic energy from the blow (or equivalent) must be discretely, finitely and efficiently absorbed by the head and brain so as to trigger the various intracranial stresses, strains, waves and motions responsible for the concussive state. It follows, therefore, that if the head is struck by a somewhat larger missile than the bullet but one that is traveling at a lower speed, concussion may now ensue, even though the overall force was the same in both conditions.

The principles and behavior of kinetic energy also account for those instances where an apparently standard accelerative or decelerative blow fails to produce a concussive response. For example, if the head is not mobile or is in contact with another surface or object, the kinetic energy transferred via the blow will simply flow through it and be transmitted elsewhere leaving the brain unharmed and its function intact. This is the reason why Denny-Brown and Russell (1941) found it difficult to concuss an animal when

its head was fixed. It similarly explains why a victim of an assault who keeps his head still by maintaining it in contact with the ground or a wall is also unlikely to lose consciousness. There are also examples of this phenomenon from sport such as where a boxer will attempt in vain to knock out his opponent when the blow is hammered on to the top of the head rather than to the side or underneath. In football, a player may escape being concussed or dinged if he tenses his neck muscles prior to collision so decreasing head mobility and allowing kinetic energy to be dispersed throughout the whole body and not confined to the head (Cantu, 1992). In all these examples, the mass of the head has effectively become too large to be easily and suddenly accelerated or decelerated by the potentially concussive force. These and other relationships between kinetic energy and concussion are displayed clearly although somewhat facetiously in a paper by Parkinson (1982).

An accelerative/decelerative injury can be inflicted via two methods: impact or impulse. Impact, as the name implies, entails a concussive blow which makes direct contact with the head. Impulse refers to an accelerative force which sets the head in motion without directly striking it. The advantage of the latter is that it allows the study of accelerative trauma without contamination by impact mechanics (Ommaya and Gennarelli, 1974). Irrespective of how the concussive insult is delivered, it exerts its effects via a process of inertial (or accelerative) loading. Inertial forces possess two principal components. These are translational or linear acceleration (or deceleration) and rotational or angular acceleration (or deceleration). Translation of the brain may be defined as movement in a straight line which passes through the head's center of gravity. In clinical concussion, this would be exemplified by a blow delivered straight into the face (Unterharnscheidt, 1975). In contrast, rotation of the brain occurs when the head is accelerated tangentially and moves through an arc around its center of gravity. In clinical concussion, this would be exemplified by a swinging upward blow to the chin (an uppercut).

The relative contribution of angular and linear acceleration to the induction of concussion remains a matter of contention. In clinical concussion, both kinds of inertial movement and stress probably co-exist and are active (Shetter and Demakas, 1979). Nevertheless, in primate head injury models where the two components of inertial loading have been experimentally isolated, it has been demonstrated that it is angular acceleration which is solely responsible for producing the loss of consciousness of concussion (Ommaya and Gennarelli, 1974). This was assumed to be mediated via shearing strains and stresses occurring maximally at the periphery (i.e. the cortex) which is also in accordance with the predictions of Holbourn's physical modeling experiments. Translational acceleration generated focal contusions and hemorrhage but no loss of consciousness.

Regardless of the precise role played by translation or rotation, it is clear that the energy imparted by acceleration of the head sets the brain in motion. The brain floats or is suspended in a protective cocoon of cerebrospinal fluid (CSF) within the subarachnoid space which allows it some freedom to move. Due to its gelatinous and viscoelastic properties, it is relatively incompressible but readily distortable (Holbourn, 1943). It therefore responds to a sudden change in the velocity of the head by oscillating, gliding, rotating, swirling or spinning within the cranial vault (Shelden et al., 1944; Pudenz and Shelden, 1946). Normally, the brain is shielded from dashing itself against the walls of the skull by the cushioning properties of the CSF and its external protective coverings or membranes. However, if the momentum becomes more forceful, the brain will come into violent contact with the bone of the skull causing deformation, distortion or compression of neural tissue. More severe jolting or jarring of the head due to the accelerative trauma is likely to result in contusions or lacerations. At least two characteristic types of injuries are recognized as occurring under these conditions: coup and contre-coup (Ommaya et al., 1971; Schochet and McCormick, 1979). With regards to just the pattern of injury, they appear to have a quite distinct pathogenesis. Coup injuries are those which are maximal directly beneath the point of impact on the skull. They tend to be associated with acceleration trauma. By contrast, contre-coup injuries occur elsewhere on the surface of the brain, most conspicuously opposite to the site of cranial impact. They tend to be associated with deceleration trauma. The mechanism of action of such lesions is controversial and not well understood, especially with regard to contre-coup injuries. To some extent both types of injuries are probably related to the relative inertia of the brain following head acceleration/deceleration. With sudden acceleration trauma, movement of the brain will lag behind that of the skull. Conversely, with deceleration injury, the brain continues to move for a fraction of a second after the skull has been abruptly halted. Another factor might be the relative distribution of CSF depending upon whether the head is in motion or is at rest when the concussive blow is struck (Cantu, 1992). A brain surface temporarily deprived of its normal concentration of shock-absorbing CSF might be more vulnerable to a particular type of accelerative/decelerative injury.

Abrupt movement of the head due to inertial (accelerative/decelerative) forces can be responsible for more than just coup and contre-coup types of injuries. Rotation of the cerebrum about its junction with the fixed brainstem may also produce stresses and strains within cortical, subcortical and brainstem pathways. Two principal types of strain arising from an applied force may be operative. These are shearing or tearing and stretching or tensile. Activity in the midbrain and upper brainstem concerned with the maintenance of alertness and responsiveness might therefore be vulnerable to mechanical disruption by these stresses and strains. Further, in higher primates including man, the rostro–caudal axis of the cerebrum crosses at almost right angles that of the brainstem–spinal cord axis (Ommaya et al., 1964; Ommaya, 1966). Such an anatomical arrangement

means that rotational forces may create proportionately greater traction within the tissues of the brainstem and consequently a more serious impairment of function in comparison with quadrupeds. It is sometimes believed that this is an important reason why more severe types of blunt head trauma cannot be easily replicated in lower mammals.

A third type of mechanical brain injury implicated in concussive injury is that of compression of the skull (Stalhammar, 1990). Advocates of this mode of action have been common but its most ardent support has been from Gurdjian and co-workers (Gurdjian et al., 1953, 1954, 1955, 1958; Gurdjian and Lissner, 1961; Gurdjian, 1972). The basic notion underlying this idea is that a traumatic blow suddenly but temporarily indents or bends the skull at the site of impact without fracturing it. This produces an immediate change in intracranial volume, brain compression and the consequent generation of pressure waves and pulses. These may then be transmitted diffusely within the cranial vault with a particular destination being the brainstem and the cranio-cervical junction (McIntosh et al., 1996). Injurious pressure gradients may be set up associated with tissue shift or deformation and shearing stresses. It is thought that similar transient increases in ICP with resultant propagation of shock waves may also be induced by inertial forces.

A fourth possible biomechanical factor in the induction of concussion involves sudden movement of the head about the neck similar to that which occurs in severe whiplash injury (Friede, 1961; Ommaya, 1966; Nilsson et al., 1977). Under these conditions, hyperextension followed by flexion of the head and neck produce stresses and strains at the craniospinal junction. These are assumed to interfere with brainstem function by distorting, displacing or stretching its neural elements.

In summary, at least four relatively distinct biomechanical processes which might be involved during the induction of a concussive state have been identified. These are: (1) violent impact between the surface of the brain and the skull due to rotatory inertial loading of the head; (2) traction on brainstem neurons due to forceful movement of the hemispheres; (3) depression of the skull bone associated with deformation of the underlying brain tissue and the propagation of ICP waves; and (4) acceleration of the head about the axis of the neck. What these last three have in common is that they all conceive concussive forces finally acting via disruption of brainstem activity. This would be consistent with the widespread and conventional understanding that a state of concussion is mediated or underlain by paralysis of brainstem function. Still, it is by no means certain that all the biomechanical factors outlined above are necessarily operating following even a standard accelerative/decelerative brain injury. Likewise, it has proven difficult to determine which of them plays a dynamic and essential role in the induction of concussion and which are simply consequences of the applied mechanical load.

3.1. The fluid percussion model of concussion

The relationship between concussion elicited by impact acceleration and that of compression of the brain has remained contentious (Foltz and Schmidt, 1956). Nevertheless, the latter seems to reproduce very similar neurological, physiological and pathological changes to those observed with the former (Sullivan et al., 1976; Dixon et al., 1987; Hayes et al., 1989; Povlishock and Coburn, 1989; Anderson and Lighthall, 1995). Of the various types of experimental compressive concussion which have been developed over the last century, the most successful has been the fluid percussion model of brain injury. The prototype was devised by Lindgren and Rinder in Sweden during the 1960s (Lindgren and Rinder, 1969; Rinder, 1969). With their device, a brief mechanical load was able to be applied to the intact dura of the rabbit. This was executed by the rapid introduction of a small fixed volume of saline into the epidural space resulting in sudden compression and a rise in ICP. This procedure duplicated many of the features of concussion associated with conventional acceleration impact to the intact skull. Lindgren and Rinder's technique was subsequently modified so as to be used with both cat (Sullivan et al., 1976) and rat (Dixon et al., 1987). With this refinement, a transient hydraulic pressure pulse was generated by striking the plunger (piston) end of a saline-filled reservoir with a pendulum. The pressure pulse was then transmitted into the closed cranial activity through a craniotomy. Impact between the fluid pressure wave and the dura elicits a sudden change in intracranial volume. Such contact triggers elastic deformation, displacement and distortion of neural tissue associated with mechanical stresses which are conducted throughout the brain.

The extent of the injury or dysfunction achieved by the fluid percussion device is dependent upon the magnitude of the hydraulic pressure wave. With a high peak pressure, severe structural damage can result, especially involving the brainstem. However, with a more moderate peak pressure, many of the symptoms of simple clinical concussion can be readily simulated. This includes immediate loss of responsiveness, flaccidity and abolition of reflexes, as well as disturbances in cerebrovascular, metabolic, respiratory and memory functions plus longer-term cognitive and behavioral disorders (Hayes et al., 1989). All of these may occur in the absence of overt histopathological changes.

Variations of the fluid percussion technique are now the most commonly used model for the experimental induction of concussion as well as for TBI, in general. In the present review, the majority of the more contemporary studies which are discussed have employed this device. The principal advantages of the fluid percussion model have been summarized elsewhere (Dixon and Hayes, 1995) but perhaps the overriding reason for its popularity is that it allows acute biological and behavioral responses to be much more easily and simply obtained from a fixed head than when it is free to move (Meyer et al., 1970; Stalhammar, 1990). A detailed

discussion on the utility and recent developments in the use of the fluid percussion technique can be found in the relevant chapters of Narayan et al. (1995).

4. The effects of concussion on neurophysiological activity

4.1. EEG and concussion

4.1.1. Background

The EEG embodies the spontaneous rhythmic bioelectrical potentials which arise from the cortex. The exact electrogenesis of the EEG still remains uncertain (Lopes da Silva, 1991). Nevertheless, a common understanding is that it reflects the temporal and spatial summation of slow post-synaptic dendritic potentials especially those associated with pyramidal neurons (Schaul, 1998). The EEG may be synchronized or desynchronized depending upon the operation of subcortical pacemakers or by intrinsic self-organizing cortico-cortical processes (Driver and MacGillivray, 1982; Fisch, 1991). The English physiologist and surgeon Richard Caton (1842–1926) is usually given the credit for making the first recordings of electrical activity from the cortex in animals during the 1870s (Caton, 1875; Brazier, 1961). However, the EEG was effectively rediscovered by the German psychiatrist Hans Berger in the earlier part of the 20th century. He described the first recordings of the EEG from the human scalp in a series of papers beginning in 1929 (Brazier, 1961). Berger also thought up the term electroencephalogram. Adrian and Matthews (1934) subsequently confirmed and extended Berger's findings. It is hardly surprising, therefore, that with the upsurge of interest in experimental concussion in the early 1940s, the relatively novel technique of EEG recordings should have been incorporated into the methodology. As Ommaya and Gennarelli (1976) have pointed out, the EEG represents a more primary and direct measure of cerebral function than secondary indices such as ICP and CBF. In addition, the EEG provides a neurophysiological correlate of the subject's level of arousal or consciousness. Recording the EEG should therefore serve as an ideal non-invasive means of gaining insights into the acute pathophysiology of concussion.

4.1.2. EEG and clinical concussion

As well as the studies of the EEG and experimental animal concussion which will be discussed in the Section 4.1.3, there was concurrently a number of attempts to record the EEG acutely from humans who had recently suffered a concussive injury. Typically, this ambitious and rather daunting research involved boxers who had been knocked out in the ring or workers who had sustained a head injury following an industrial accident (e.g. Dow et al., 1944; Kaplan and Browder, 1954; Larsson et al., 1954; Pampus and Grote, 1956). Initial EEGs recorded under such conditions were often obtained within minutes of trauma. Disappointingly, these traces revealed little evidence of residual abnormalities in cerebral activity, even at an early stage. For example, Dow et al. (1944) set up a laboratory in a shipyard and so were able to make EEG recordings from head injury victims in some instances as early as 10–15 min post-trauma. EEGs were recorded from over 200 patients but not all had been concussed judging by a lack of memory loss or unconsciousness. In the majority of subjects, little or no alteration in EEG activity could be detected. For the remainder, the most notable abnormality was a diffuse slowing of cerebral rhythms with an increase in theta and delta activity. This type of pattern was most prominent in recordings made soon after head injury and soon resolved. In some patients who had been genuinely concussed, the EEG was within normal limits even when the initial recordings were made within 15 min of injury. Judging solely from these recordings, there was little evidence of a gross disturbance of cerebral activity following concussion. Subsequently, Kaplan and Browder (1954), Larsson et al. (1954) and Pampus and Grote (1956) recorded EEGs from boxers shortly after they had been knocked out. All described a slightly disorganized EEG which could include a generalized diminution in voltage and a slowing in some rhythms.

Interesting as these attempts were, it soon became apparent that such investigations were unprofitable endeavors. Even when recordings began almost immediately after recovery from the head injury, the EEG was able to provide little or no insight into the acute pathophysiology of concussion (Dawson et al., 1951). So far as it is known, the EEG has never been recorded from a human subject during an actual concussive event (West et al., 1982). The general failure of the clinical studies reinforced the conviction that animal models of concussion were vital in order to obtain this information.

4.1.3. EEG and experimental concussion

The earliest attempt to quantify the effects of experimental concussion on the EEG was made by Williams and Denny-Brown (1941). Their study was published simultaneously with that of Denny-Brown and Russell (1941). Subjects were cats which were lightly anesthetized with pentobarbital. Acceleration concussion was produced by striking the occiput with a pendulum hammer using the same technique as employed by Denny-Brown and Russell. The result was an immediate generalized loss of amplitude in the EEG with the higher frequencies being the most vulnerable to the concussive blow. In some instances the suppression of the EEG was so marked as to appear isoelectric. During the recovery phase, slow delta waves appeared in the record. By the end of this period, the EEG rhythms began to return to an approximate baseline pattern. Restoration of reflex activity coincided only roughly with these post-traumatic changes in the EEG. The initial attenuation in voltage could persist for up to about 3 min. There was, nonetheless, considerable variability among animals, at least part of which can be accounted for by variations in the force of the concussive blow. In addition, animals were subject to multiple blows

(and recordings) often in relatively quick succession. Although Williams and Denny-Brown observed essentially the same EEG findings irrespective of how many blows had been administered, it might be wise to discard from consideration any data recorded after the first concussion. The EEG findings, especially the near instant decrease in cerebral activity, were interpreted as evidence for Denny-Brown's theory that the pathophysiological basis of concussion consisted of a brief direct traumatic disruption of neural function.

Within a relatively short time, Walker et al. (1944) ignited a controversy which endures to the present day. Subjects for their experiments were cats, monkeys and dogs and a variety of mechanical techniques were employed to concuss them. The one that proved most useful and reliable was a device designed to produce compression concussion (a precursor of the contemporary fluid percussion injury device). In order to elicit concussion in their animals, Walker et al. applied a water pressure pulse directly to the exposed and intact dura. The percussive blow was delivered while the subjects were curarized and under local anesthesia but otherwise awake. Straight after the blow, there was a high voltage electrical discharge (up to 1 mV) followed by an after-discharge consisting of high frequency spiking in the EEG. This activity endured for 10–20 s. The epileptic-like discharge then subsided and after a short period of extinction, the normal EEG gradually returned over a period of minute. In animals which were not curarized, the compressive impact was associated with convulsive movements which had both tonic and clonic components in the case of cats but usually just a tonic phase in monkeys. Neither the motor nor the electrical seizure activity was present when the animals had been anesthetized with pentobarbital presumably because of its anti-convulsant properties. Both the work of Denny-Brown and Walker agree that spontaneous EEG activity is markedly depressed for a relatively short period following a concussive blow. The findings of Walker and co-workers are otherwise quite incompatible with Denny-Brown's theory that the trauma of a concussive blow causes an instant paralysis of cerebral function. Instead, they suggest that the brain's immediate response is one of intense generalized neuronal excitation.

Dow et al. (1945) attempted to reconcile the conflicting reports of Williams and Denny-Brown (1941) and Walker et al. (1944). Unfortunately, their findings did little to resolve the problem. Subjects for their experiments were mostly dogs but also included a small number of cats. They were allegedly concussed using a pendulum device while under either general (barbiturate) anesthesia or local (procaine) anesthesia. Not surprisingly, those animals which were under general anesthesia suffered a greater concussive episode than those which were awake. The most characteristic response from the former group was an immediate but transient loss or attenuation in higher amplitude spindle-like activity. Spindles are short bursts of rhythmical cortical activity normally associated with the lighter stages of sleep. Sometimes there was a more generalized suppression in the EEG affecting all rhythms. This period could persist for up to 1 min and might be followed by a longer but variable span of slow wave activity similar to that described by Williams and Denny-Brown. In contrast, the most marked alteration in the awake subjects was a reduction in the normal fast low voltage activated EEG which was sometimes intermingled with slow activity. This state normally lasted for only a few minutes but could endure for an hour. A subsequent period of slow wave activity did not follow under these circumstances. There was considerable diversity among these post-concussive electrical patterns and in many recordings (particularly in the locally anesthetized group), the traumatic blow had little effect on the EEG. There was never any sign of epileptic-like activity in the post-concussion tracings comparable to the discharges found by Walker et al. (1944), irrespective of whether the animal was anesthetized or awake. Instead, it was concluded that the findings were rather more consistent with the acute depression in EEG activity described by Williams and Denny-Brown (1941). It should be noted that despite multiple recordings, just three examples of EEG tracings after concussion were actually illustrated in this paper.

Dow et al.'s study is of an often confusing nature and this and other limitations make interpretation of it difficult. For example, although only 19 animals were employed they nonetheless provided the material for 107 separate experiments. This meant that individual animals may have been the subject of repeated concussions but the conditions (especially the timing) under which they were traumatized are often unclear. Nor is the cumulative effect of serial concussions considered although, to be fair, this seemed a common pitfall in similar experiments conducted about this time (e.g. Denny-Brown and Russell, 1941). A further complication is that no consideration is given to the extent to which procaine infiltration of the scalp or initial ether anesthesia for electrode insertion might have confounded the impact of the concussive blow and therefore any modification of EEG activity. In addition, movement artifact blocked amplifier function for the first few seconds after concussion in a similar fashion to what also occurred in Williams and Denny-Brown's study. As the authors admit, their data can therefore provide little or no insight into the most acute EEG changes following concussion. Finally, it is also acknowledged that the pendulum may more often than not have failed to deliver a genuine concussive blow. These types of flaws and shortcomings weaken the author's contention that their results can provide no evidence in favor of post-concussion excitation in the EEG.

A subsequent experiment by Ward and Clark (1948) also basically reconfirmed the findings of Williams and Denny-Brown (1941) and Dow et al. (1945). In this experiment, subjects were solely cats who were concussed under different levels of barbiturate anesthesia. Both accelerative and compressive methods of concussion were employed. Some animals were struck on the head with a hammer or a dropped weight. In others, a fluid percussive device not unlike that utilized by Walker et al. (1944), was employed. Irrespective

of the technique, very similar EEG findings were reported. There was an immediate attenuation in voltage followed by the quite rapid appearance of irregular fairly high amplitude theta and delta waves and a progressive return to baseline patterns, usually within a short time. Some evidence of possible acute excitatory activity was also observed under certain conditions (light anesthesia, multiple blows, increased ICP). This was manifested by low voltage fast activity and sharp waves in the EEG.

During the 1950s, a limited number of papers revisited this problem but failed to reach any consensus. The most widely cited study is that of Foltz et al. (1953). Subjects were 19 cats and 1 monkey whose heads were accelerated using a gas-operated piston. Some animals experienced more than one concussive blow. EEG recordings were made from the moment of impact but failed to detect any evidence of epileptiform activity even during the first few seconds following the concussive blow. Instead, the most common finding was a generalized diminution in amplitude lasting about 10 min reminiscent of the recordings obtained by Williams and Denny-Brown (1941). In other animals, little alteration in the EEG could be discerned at all. Unfortunately the authors presented acute data from just 2 of 24 recordings both presumably anesthetized with either vinyl ether or the diallybarbituric acid (barbiturate Dial). Similar EEG recordings were also reportedly obtained when the animals were not anesthetized but no evidence for this is otherwise presented. Nor is it made clear how the animals were immobilized under awake conditions or how soon after a prior anesthetic such "non-narcotized" recordings might have been obtained. Foltz et al. interpreted the discrepancy between their EEG recordings and those of Walker et al. (1944) as possibly due to the use of accelerative rather than compressive concussion.

Meyer and Denny-Brown (1955) repeated and extended the original experiments of Williams and Denny-Brown (1941) with essentially the same results. Subjects were both cats and monkeys anesthetized with pentobarbital. Three methods were employed to produce concussion: impact acceleration and two types of compression including a percussive device similar to that used by Walker et al. (1944). Irrespective of the technique, there was an immediate reduction in EEG activity after the head injury followed by the same pattern of recovery observed in the previous experiments. The authors could find only a single example where there was a focal discharge of epileptiform activity. They also suggested that the so-called cortical injury potential might better explain the presence of the high amplitude response immediately following the concussive blow than neuronal excitation.

During the next decade, Ommaya and co-workers began their studies of experimental concussion using primates as subjects. In their first reports (Ommaya et al., 1964; Ommaya, 1966), monkeys under light barbiturate anesthesia were concussed using the same type of gas pressure gun employed by Foltz et al. (1953). Immediately after the concussive blow, there was a marked increase in the amplitude of the EEG which persisted throughout much of the period of unconsciousness. According to the authors, this was associated with a slowing of the baseline rhythm. A retrospective analysis of their recordings suggests that any such decrease in frequency was subtle and while apparent in some traces, in others there may well have been an increase. In addition, sharply contoured potentials (or spiking) can sometimes be detected in the post-concussion traces hinting at an epileptic-like discharge. Ommaya et al. (1964) remark that their findings are congruent with neither the suppression pattern of Williams and Denny-Brown (1941) nor the excitation followed by extinction pattern of Walker et al. (1944). While this is true, the high voltage paroxysmal activity throughout the period of concussion is obviously more compatible with a state of cerebral excitation rather than of paralysis. Such a conclusion would also be supported by the convulsive movements which were sometimes reported to occur during this period (Ommaya, 1966).

A later study from Ommaya's laboratory failed to confirm these findings (Ommaya et al., 1973; Letcher et al., 1973). In this instance, the subjects were chimpanzees reputedly alert and drug free at the time of the concussion, although they had been administered a barbiturate anesthetic 24 h before. Concussive impact to the occiput was delivered by the same type of piston device used previously. On the whole, experimental concussion appeared to have minimal effect on the EEG under these conditions. There was no evidence of any increase in amplitude, activity in frontal and parietal leads remained unaltered and the only indication of flattening occurred in the occipital leads. Slow wave activity also appeared with more severe head injury. Among the limitations of this study were that only four animals were utilized, multiple blows were inflicted in some cases and initial EEG recordings were delayed (or at least not illustrated) for at least 20 s and sometimes up to 1 min following the head trauma. It is possible, therefore, that any acute excitatory activity in the EEG could have been missed. In this respect, it is of interest to note that the concussive blow was reported to be accompanied by mild convulsive movements (Ommaya et al., 1973).

Meyer et al. (1970) examined the effects of experimental concussion on the EEG of the baboon. Meyer had previously collaborated with Denny-Brown on their 1955 study. Concussion was elicited with a compressive method using an air gun and animals were anesthetized with pentobarbital. Following an injury sufficient to induce mild concussion, the EEG in the majority of animals consisted of a brief period of low voltage fast activity with a frequency between 14 and 20 Hz. This paroxysmal burst was accompanied in some animals by convulsive movements. Judging by the EEG changes, the motor phenomena, and other data, Meyer et al. (1970) concluded that the acute traumatic period was associated with a state of cerebral excitation, at least for milder forms of concussion. This EEG pattern was not observed in all subjects. Some showed no change, others

an increase in slow wave activity and the remainder a generalized depression.

Brown et al. (1972) recorded the EEG from the lightly anesthetized (with pentobarbital) guinea pig following experimental acceleration concussion. This technique was similar to that employed by Williams and Denny-Brown (1941) and so, too, were their findings. Cerebral activity was slowed and in some instances became almost isoelectric immediately after the head trauma. High voltage slow waves and then the appearance of higher frequencies in the EEG accompanied the return of normal reflex function. Quite similar findings using the fluid percussion injury device were described later on in the decade by Povlishock et al. (1979) and subsequently by Duckrow et al. (1981). Both found a transient suppression of EEG activity when using the cat as subject under barbiturate anesthesia.

Two further studies, both using spectral analysis to quantify the EEG, did little to clarify the issue of the genuine nature of post-concussive cerebral activity. In the first of these, Sullivan et al. (1976) elicited compression concussion in anesthetized cats using fluid percussion. In the second, West et al. (1982) concussed awake rats using an impact acceleration technique. Despite such differences, very similar findings were reported with both studies demonstrating an immediate decrease in the power of all EEG frequencies following the concussive blow. Although the rats in West et al.'s experiment regained spontaneous movements within 0.5 min, EEG amplitude abnormalities did not peak until about 5 min. In both the cat and rat studies, the generalized depression in amplitude gradually recovered, taking some 2 h in the case of the rat. Neither study detected any electrographic evidence of seizure activity. Despite this, some animals in West et al.'s experiment did display convulsive movements. This could imply that analyzing the EEG power spectrum following concussion may not be a sensitive or appropriate method for detecting the presence of epileptiform activity. It should also be taken into account that because of technical difficulties, EEG recordings did not begin immediately after the head trauma and may have been delayed for several seconds. Any expected convulsive activity may have begun to decline by then as the concussive blow inflicted in the West et al.'s study did not appear to be especially hard.

The four most recent studies of the effects of experimental concussion on the EEG have all provided evidence of a state of cerebral hyperactivity during the acute post-traumatic period. First, Dixon et al. (1987) usually recorded an approximately 20 s episode of epileptiform activity in the anesthetized rat following fluid percussion injury. Interestingly, this spiking activity did not begin immediately after the brain injury. Following this discharge, the EEG remained depressed for at least 10 min. Similar evidence of neuronal excitation was described by Hayes et al. (1988). Subjects were cats anesthetized with nitrous oxide. Immediately after fluid percussion concussion, there was a brief increase in higher frequency activity which coincided with the period of reflex paralysis. A small group of chronically prepared cats were concussed while awake as a control for the effects of anesthesia. Similar findings were reported for these animals, with no evidence of acute slowing or depression of the EEG. Both Dixon et al. (1987) and Hayes et al. (1988) had employed the fluid percussion device. In contrast, two further investigations into this problem used a type of weight drop technique. In one, Marmarou et al. (1994) produced acceleration concussion by striking the helmeted head of an anesthetized rat with a brass weight. The animal's head rested on a foam cushion and was therefore free to move. Epileptiform discharges occurred for up to 1 min after the blow followed by a period of diminished EEG activity for 10 min. Normal rhythms were restored during the next 20 min. Convulsive movements occurred during the first 15–30 s following head trauma. In the second, Nilsson et al. (1994) used a weight drop device to produce compression rather than acceleration concussion. This was accomplished by allowing a weight to fall onto a piston in contact with the dura of an immobilized anesthetized rat. Of the 17 animals utilized, all but 3 displayed bilateral seizure activity in the EEG for about 1 min following the traumatic impact. This discharge consisted principally of generalized high voltage spiking which fairly abruptly segued into a period of post-ictal depression. Like that reported by Dixon et al. (1987), there was a delay in the onset of epileptiform activity in the EEG following the concussive insult. There is no ready explanation for this phenomenon although it may be notable that both studies employed nitrous oxide as the anesthetic, but so did Hayes et al. (1988).

The studies summarized above do not comprise a definitive list of the effects of experimental concussion on the acute EEG. Nonetheless, they do represent the main findings which have emerged from such experiments. As several previous reviews on this subject have detailed (e.g. Kooi, 1971; Stockard et al., 1975; Shetter and Demakas, 1979; Bricolo and Turella, 1990), such investigations can be fairly evenly bifurcated into those which have described an immediate post-concussion depression in the EEG and those which have found an initial period of excitation occurring prior to a longer period of attenuated or suppressed cerebral electrical activity. Although there otherwise exists little consensus on this matter, determining which of these neurophysiological states actually underlies concussion may be the key to understanding its pathophysiology. One aspect on which there should be agreement is that it would seem quite anomalous if the pathobiological processes governing concussion could be associated, on occasion, with both near extinction and excitation of neuronal function. Rather more likely is that only one of these states represents the genuine reaction of the central nervous system to the concussive blow while the other is simply an artifact due to the exigencies of the methodology.

There is also no reason to believe that the method of concussion (i.e. compression versus acceleration) could account for the discrepant EEG findings as Walker (1994) suggested. It is true that paroxysmal excitation has been

more often observed following compression concussion and conversely that an attenuated EEG has been more commonly recorded following accelerative trauma. Nonetheless, any such trend is most likely artifactual or accidental and therefore misleading. It is, for example, a good deal easier to accurately deliver a calibrated blow using a compressive set up in comparison with the cruder and less reliable acceleration/deceleration methodology. Also, it is technically much less demanding to obtain acute EEG recordings following a concussive insult when the head is fixed than when it is mobile and unrestrained. Finally, there are reports where attenuation or extinction of cerebral activity has followed compressive concussion and vice versa.

Assuming the brain's response to concussion is a standard or uniform one, then it remains a puzzle as to why it has proven such an intractable problem to determine the immediate EEG changes in a definitive manner. As noted above, probably a number of factors have contributed to this. Be that as it may, the principal one is undoubtedly the virtual necessity when recording activity such as the EEG to immobilize the animal in some manner. The simplest and most common method of achieving this is by the administration of a general anesthetic. It therefore seems reasonable to suppose that it is the concurrent anesthesia or its lingering after-effects which is the factor most responsible for the contradictory EEG findings immediately following the concussive insult. The EEG is particularly sensitive to a wide range of neuroactive drugs (Kooi, 1971; Dyro, 1989). Anesthetics, such as the widely used barbiturates, can have potent but variable dose-dependent effects on the EEG. Characteristic effects of barbiturates on the EEG at therapeutic doses are initially an increase in fast beta activity followed by slower spindle-shaped bursts. At higher doses, there is a progressive generalized slowing of cortical rhythms and intervals when the EEG is suppressed (Clark and Rosner, 1973; Fisch, 1991).

Anesthetics probably contaminate the acute post-traumatic EEG in three related ways. The effects of the medication and of the concussion may interact or interfere with one another to modify the EEG. Alternately, the effects of the medication may override and therefore disguise those of the concussion. Finally, the powerful anti-convulsant properties of some anesthetics, such as barbiturates, may neutralize or suppress any epileptiform activity. It therefore seems reasonable to assume that it is the masking or dampening influence of the anesthesia which is most responsible for the depression in voltage and slowing in frequency of cortical rhythms which have often been reported since the original description by Williams and Denny-Brown some 60 years ago. It is remarkable that there is not a single documented (i.e. illustrated) example of a post-concussive loss or suppression of EEG activity which cannot, in principle, be accounted for by the confounding effects of medication. It should also be recalled that Walker et al. (1944) recorded evidence of post-concussive seizure activity in the EEG only when the subject was awake but the effect was not evident when the animal was anesthetized with a barbiturate.

If the interpretation outlined above is correct, then it logically implies that the genuine cerebral state immediately following a concussive blow must be excitatory in nature. If such a neuroexcitatory hypothesis is correct, then it would be predicted that epileptiform discharges should never fail to materialize nor should the acute EEG ever be suppressed or attenuated following a concussive blow in an awake (non-medicated) animal. Unfortunately, determining the validity of such an assertion is hampered by the scarcity of such recordings. Nevertheless, at the least, it can be safely said that there is as yet no direct, unequivocal and available data which can refute this prediction.

In addition, there is now quite a large body of evidence which demonstrates that epileptiform activity can arise in the post-concussive EEG even when the subject is currently at least lightly anesthetized. In this case, it must be assumed that the balance between the effects of concussion and the effects of the medication on the EEG has shifted in favor of the former. Under these conditions, it appears that the comparatively weak medication is unable to dominate or extinguish the more robust and energetic excitatory activity in the EEG. There is also a second consideration when attempting to reconcile the discrepant post-concussive EEG findings. This is the delay which has sometimes occurred following the delivery of a concussive insult before an adequate EEG signal can be obtained. While such a delay is typically of only a few seconds duration, it may nonetheless be sufficient to conceal any immediate seizure activity. This shortcoming was also identified by Foltz et al. (1953) who pointed out that in Williams and Denny-Brown's study, post-concussive blocking of the amplifiers meant that an EEG trace could not be re-established until up to 10 s after the administration of the blow. As summarized in the present section, there have since been a number of occasions when EEG recordings have been similarly delayed. All have involved the use of accelerative-type techniques.

In conclusion, a careful analysis of the EEG studies makes it seem more likely that concussion is accompanied by an initial state of excitation rather than inhibition or paralysis of cerebral function. This indicates that the concussive blow must trigger a brief period of intense generalized neuronal discharge. Those studies which found evidence of depressed cerebral electrical activity can all be more or less satisfactorily explained by anesthetic protocols or methodological limitations such as delayed time of onset of recordings and the cumulative effects of multiple concussive blows.

4.2. Evoked potentials and concussion

4.2.1. Background

A sensory EP, as the name implies, is a bioelectrical response which is deliberately elicited by feeding a stimulus into the nervous system. It differs from spontaneous electrical activity not only in this respect but also because the

generally smaller voltage of the EP tends to be swamped by the higher amplitude EEG. In addition to discovering the EEG, Richard Caton is usually given the credit for making the first cortical EP recordings in the 1870s (Stevens, 1973; Brazier, 1984). Caton obtained EPs from the exposed cortex in a variety of animals including rabbits, monkeys and cats. With appropriate electrode positioning, he observed sudden changes in electrical potential following stimulation of both limb and eye. Before the end of the century, Caton's discoveries were independently confirmed by the Polish physiologist Adolph Beck (1863–1939) (Brazier, 1984). Using dogs and rabbits as subjects, Beck managed to record not only visual and somatosensory types of EPs but also auditory potentials, a feat which had eluded Caton. In spite of this early work, it was not until after the World War II that it became feasible to make non-invasive recordings from skull or scalp locations. This capability arose mostly from the invention by the English physiologist George Dawson of an electromechanical averager (Dawson, 1951, 1954). Dawson's technique made use of the fact that, unlike the randomly distributed EEG and any concomitant muscle activity, an EP would always be time-locked to the onset of the sensory stimulus. Summing and averaging multiple responses to the stimulus should enable the background activity to cancel itself out while the EP becomes progressively better defined. By the end of the 1950s, the extraction of EPs via signal averaging became a more practicable procedure with the development of the average response computer by Clark and co-workers at MIT (Brazier, 1984). This advance paved the way for the widespread use of EPs for both clinical and experimental purposes (Regan, 1972).

There are at least two notable aspects concerning studies of the effects of experimental concussion on EPs. First is the comparative dearth of such investigations compared with those of the EEG. This is somewhat surprising for a number of reasons. One is that recording EPs is not much more technically demanding than that of the EEG. A second is that EPs are much less susceptible to anesthesia and other medications which so confound EEG studies. A third is that EPs may provide worthwhile information about the site and nature of changes in cerebral activity not obtainable with the EEG. It may also be of incidental relevance that the prognostic value of some types of EPs is much superior to that of the EEG when used to assess severe head injury in patients (e.g. Hutchinson et al., 1991). At least part of the discrepancy between the number of EP and EEG studies can, of course, be accounted for by the more than a decade's head start that the EEG studies had over those of sensory EPs.

A second feature is the preponderance of experiments which have employed the somatosensory EP (SEP) in preference to auditory or visual types of EPs. The reasons for this option are probably related to why SEPs are also the EPs of choice when recordings are made from patients with severe head injury (Judson et al., 1990). First, the somesthetic pathways traverse the entire length of the brain so that a cortical SEP is a measure of activity occurring over a wide expanse of neural tissue. Second, the somatosensory cortex is relatively accessible in most mammals, allowing the cortical SEP to be readily obtained with an extradural or surface electrode. Third, stimulating a peripheral nerve electrically by-passes the normal transduction process and therefore makes attempting to elicit a SEP immediately after the head injury a more dependable and invariable procedure (Cant and Shaw, 1986).

4.2.2. Somatosensory evoked potentials and acceleration concussion

The earliest report of the effects of experimental concussion on SEPs was that of Foltz and Schmidt (1956). Their experiments took place against a background where Moruzzi, Magoun and co-workers were beginning to unravel the organization of the ascending reticular activating system (ARAS) and its role in the modulation of consciousness (Moruzzi and Magoun, 1949; Lindsley et al., 1949). The ARAS mostly occupies the more rostral portion of the reticular formation. The reticular formation is a polysynaptic network of many short neurons and interneurons in the core of the brainstem and midbrain. The operation of the ARAS, its complex reciprocal relationship with its associated thalamic nuclei and its control over level of cortical activity and arousal via diffuse thalamo-cortical projections will be discussed in greater detail in Section 5.2 on the reticular theory of concussion.

In a previous study, Foltz et al. (1953) had observed not only a depression of cortical activity following concussion in the monkey but also a proportionately more severe reduction in the electrical activity within the reticular formation. It followed therefore that the pathophysiology of concussion might involve inactivation of the ARAS which in turn would precipitate a loss of consciousness. Foltz and Schmidt reasoned that such an impairment of reticular activity could be either direct or indirect. It might, for example, represent a more or less direct impact of the concussive blow on the function of the ARAS. Alternatively, it could disrupt the transmission of afferent signals within the specific sensory pathways. The reticular formation is normally innervated by such activity via collaterals branching off the lemniscal and extra-lemniscal pathways. These two possibilities were tested by recording SEPs arising in the reticular formation and the medial lemniscus following impact–acceleration concussion in the rhesus monkey. The authors did not use signal averaging techniques to obtain their SEPs but instead recorded responses to a single electrical shock of the sciatic nerve.

Following head injury, the short latency lemniscal SEP was invariably present and seemingly intact. In contrast, the longer latency reticular SEP was always lost or at least very attenuated in amplitude. In one animal, the gradual recovery of the reticular SEP was monitored until it presumably returned to normal 20 h after the concussion. The findings of this experiment therefore suggested that activity in the brainstem was differentially sensitive to the effects of concussion with that arising in the medial lemniscus virtually

immune while that in the reticular formation being very vulnerable. The results were therefore consistent with the hypothesis that the concussive blow immediately, specifically and directly targets neurons of the brainstem reticular formation (BSRF).

Foltz and Schmidt's experiment is one of the most frequently cited studies in the concussion literature. It is also thought to provide one of the key pieces of evidence in favor of the widely held notion that concussion involves impairment or disruption of the ARAS, i.e. the reticular theory of concussion. It is disappointing that the methodological flaws and other limitations of this study are so pronounced that they render most of its conclusions invalid. First, the authors offer very little data in support of their conclusions. Although eight animals were utilized, only a single recording from a single animal illustrates the differential loss of amplitude of the brainstem potentials and no group data is provided. There was also no baseline recordings available for comparison as the intracranial electrodes were inserted only after the concussive blow had been delivered. Unfortunately, it took at least 20 min for the electrodes to be stereotaxically implanted following head trauma and so there was a substantial delay before the first SEP recording was possible. This leaves the conclusion that the medial lemniscal response was preserved following concussion unsustainable. No inference can be made with any certainty about the status of either potential during the immediate post-concussive period.

There is also some doubt over exactly what state of consciousness the animals actually were in when the SEP recordings began. Judging by other studies of concussion in primates, such as those subsequently discussed in this section, impact acceleration would probably knock out an awake monkey for only a few minutes, at most. In this respect, it is notable that the authors found it necessary to immobilize most of their subjects with dihydro-β-erythroidine before satisfactory recordings could be made. If the animals had, in fact, recovered awareness or responsiveness by the time of the first recordings, then it would be quite spurious and unwarranted to draw any conclusions from the SEPs about the role of the BSRF in the pathogenesis of concussion. In the case of the animal which was followed for 20 h after trauma, it was impossible to correlate the SEP recordings with behavioral state as the subject was under neuromuscular paralysis. It is also a pity that the authors did not simultaneously record the cortical SEP so as to ensure that the putative reticular SEP was not simply an artifact generated by far field cortical activity. In summary, Foltz and Schmidt could well have been correct that a loss of sensory driving within the ARAS is principally involved in the coma of head trauma. Regrettably, their findings provide little or no incontestable evidence in support of such an assertion.

During the following decade and a half, there were no further attempts to explore the relationship between EPs and experimental head trauma. Then in 1973, Ommaya's team succeeded in simultaneously recording both the EEG and the SEP from the chimpanzee (Ommaya et al., 1973; Letcher et al., 1973). Unlike Foltz and Schmidt (1956), signal averaging procedures were used to obtain the cortical SEP following median nerve stimulation. The use of chronically implanted epidural electrodes to record the cortical response meant that SEP measurements could begin almost immediately after the head blow (i.e. within 1 min). While the EEG was relatively unaltered by the head injury, there were quite pronounced changes in the SEP. A standard concussive blow seemed to temporarily destroy at least the early components of the SEP. A more powerful blow caused a total abolition of all the SEP components. A less potent blow which simply stunned the animal produced an overall reduction in amplitude without loss of components. The general principle appeared to be that the greater the concussive force, the greater the distortion to the SEP waveform. The persistence of this abnormality correlated strongly with the duration of the period of unconsciousness. Unlike Foltz and Schmidt's brainstem SEPs, there was no evidence that some components of the cortical waveform were more or less sensitive to closed head injury. As the authors pointed out (Letcher et al., 1973), the early components of the SEP are generated by the arrival in the primary receiving area of the somatosensory cortex of activity transmitted via the fast conducting lemniscal pathway. According to Foltz and Schmidt's findings, therefore, the primary component of the cortical SEP might have been expected to survive the concussion. In fact, the early components of the cortical SEP appeared to be just as much affected by the concussive blow as the later ones. This implies that activity propagated within the lemniscal system is as vulnerable to a concussive blow as that in extra-lemniscal or non-specific reticular pathways. However, the level at which such a dysfunction is occurring cannot be determined from the data of Letcher et al. Therefore, it cannot be assumed that the lemniscal potential would have been similarly absent (along with the reticular response) if Foltz and Schmidt (1956) had begun their post-traumatic recordings sufficiently early. In almost every respect, this study by Ommaya and co-workers is superior to that of Foltz and Schmidt (1956). Nonetheless, it is not without some flaws. As with the EEG recordings, there is the problem of whether lingering effects of barbiturate anesthesia may have lengthened the period of unconsciousness or else aggravated the SEP abnormalities. Also, inflicting an adequate concussive blow appeared a technically difficult task. Of the 10 chimpanzees used, only 4 proved satisfactory and in half of these multiple blows needed to be inflicted.

Shortly afterwards, Ommaya and his then co-worker Gennarelli published their celebrated article in *Brain* (Ommaya and Gennarelli, 1974). This was primarily a theoretical article and as such will be discussed in the section dealing with the centripetal theory of concussion (Section 5.3). Nevertheless, the centerpiece of this paper was yet another study of the effects of closed head injury on SEPs from the primate. In this instance, the subjects were squirrel monkeys. Ommaya and Gennarelli used an accelerating

device designed to produce non-impact inertial loading of the head. The apparatus could be modified so that the two main components of inertial loading (translatory and rotatory acceleration) could be investigated separately.

Using non-impact angular or rotational acceleration proved a much more effective and dependable technique for eliciting concussion than the more crude direct blow to the occiput (Letcher et al., 1973). Of the 12 monkeys studied, all were successfully concussed. The cortical SEP recorded from the squirrel monkey following median nerve stimulation consisted of an initial positivity (P1) followed by a more prominent secondary positivity (P2). After concussion, both P1 and P2, as well as the later slower components of the waveform, were all abolished for the duration of the loss of consciousness. Judging by the very limited data provided on this matter, this period lasted from 1 to 7 min. The return of gross responsiveness in the animal coincided with the restoration of the SEP, although the waveform subsequently remained abnormal for several h. These SEP findings therefore both confirmed and clarified the observations made under less satisfactory conditions in the chimpanzee (Letcher et al., 1973).

According to Ommaya and Gennarelli (1974), the P2 component of the SEP is generated by the arrival of afferent signals traveling via diffuse non-specific pathways functionally related to the ARAS. It follows, therefore, that the behavior of the cortical P2 component should be a reflection of the current operational state of the brainstem arousal system (i.e. the ARAS). As a consequence, Ommaya and Gennarelli argued that the loss of the P2 component signifies that disturbance of function within the BSRF plays a pivotal role in the coma of closed head injury. This conclusion based on cortical SEPs is essentially the same as that derived by Foltz and Schmidt (1956) from their brainstem SEPs.

In a second series of experiments, Ommaya and Gennarelli (1974) subjected another group of monkeys to translational or linear acceleration of the head. Under these conditions, not a single one of the 12 animals was concussed and neither was there even transient disappearance of any of the SEP components. However, the waveform did display a persistent attenuation in voltage in some components most notably that of P2. These findings therefore tended to support Holbourn's original hypothesis that at least for concussion to occur, rotational rather than linear shaking of the head was mandatory.

One of the difficulties in evaluating this data is the almost complete dearth of detail on how these experiments were conducted. In their reference list, Ommaya and Gennarelli (1974) promise at least five papers in preparation which would presumably contain this information. So far as can be ascertained, none of these has ever materialized. Ommaya and Gennarelli essentially rewrote their *Brain* article at least twice (Ommaya and Gennarelli, 1975, 1976) but none of the three versions contains information on methodology. A second problem relates to the paucity of data concerning the neurophysiological findings. The authors do provide extensive details on hemorrhages, hematomas contusions and other lesions present in each of their subjects, but only one set of EP recordings from their 12 concussed monkeys is actually illustrated. There is also a mysterious 13th animal not otherwise referred to in the text. In one of their subsequent rewrites (Ommaya and Gennarelli, 1976), a second set of SEP recordings from the rotational (i.e. concussed) group is also provided. Nonetheless, all three illustrations do show essentially the same pattern of change in the cortical SEP waveform following head trauma.

A third problem concerns the origins of the individual components of the cortical waveform and consequently the validity of Ommaya and Gennarelli's interpretation of their SEP findings. Few would argue that the P1 component is generated following the arrival of the afferent volley in the primary sensory cortex and therefore is a measure of activity propagated in the fast conducting medial lemniscal pathway (Kooi, 1971; Ottoson, 1983). By contrast, the conclusion that P2 is a reflection of activity arising within the ARAS of the BSRF is a much more debatable contention. Ommaya and Gennarelli (1974) cite the research of Singer and Bignall (1970) on the origin of the cortical SEP in the squirrel monkey. According to Singer and Bignall, the P2 component is generated by activity traveling via slower extra-lemniscal or spinothalamic tracts which might project to more widespread cortical locations than do lemniscal pathways. Activity in spinothalamic pathways (like that in lemniscal fibers) may also contribute to the activation or driving of the ARAS via collaterals which branch off the sensory tracts. Nonetheless, a careful scrutiny of Singer and Bignall's paper reveals that nowhere do these authors claim that the P2 cortical potential is a direct or indirect measure of ARAS function. Ommaya and Gennarelli's claim that the loss of the P2 component necessarily indicates significant involvement of the ARAS in the induction of concussion is therefore a conclusion without foundation. The total abolition of the early, middle and late components of a cortical EP waveform would usually indicate some form of more generalized disruption of neuronal function. This would be a simpler explanation than the hypothesis that mechanical loading of the head as occurs in concussion somehow targets a particular site or pathway within the BSRF. The temporary extinction of the entire cortical EP does not necessarily indicate that the principal site of action of concussion must reside at the cortex. Still, in the absence of any competing neurophysiological evidence, this must remain the initial and prime suspect.

A decade later, the findings of Ommaya and co-workers using primates were replicated with a rodent model of experimental head injury (Shaw, 1986a). In this instance, rats were concussed using an impact acceleration technique which did not produce such a consistent response as Ommaya and Gennarelli (1974) had managed to achieve with non-impact rotational acceleration. The range of head trauma produced was more reminiscent of Ommaya's previous experiments with the chimpanzee (Letcher et al., 1973). Nonetheless, in animals which appeared to be genuinely concussed

(yet survived), the entire cortical waveform was annihilated for up to 60 s. The waveform started to reappear in a sequential fashion with the early components being the first to re-emerge. The restoration of the late negative component (N2), although in an attenuated form, seemed to coincide with the return of wakefulness or responsiveness in the animal. The SEP findings in the rat were therefore basically the same as that described for the chimpanzee and the squirrel monkey. Among the minor discrepancies was the observation that the SEP did not return so abruptly as it did in the squirrel monkey. Also, in non-fatal concussion, it was not possible for the cortical SEP to remain absent for much more than 1 min in the rodent. In both the monkey and the rat, abnormalities in the EP waveform lingered long after recovery of consciousness or responsiveness. Three examples of the effects of experimental concussion on the cortical SEP in the rat are illustrated in Figs. 1–3. Further examples are available in the original paper (Shaw, 1986a).

The classic theory of the origins of the cortical EP maintains that it is the late slow high amplitude components (such as N2 in the rat SEP) which are generated by diffuse non-specific bilaterally projecting thalamo-cortical afferents functionally related to the ARAS. This is the so-called dual projection system theory. It arose in the early 1960s largely because of the discoveries on the role of the ARAS during the previous decade (Abrahamian et al., 1963; Rosner et al., 1963; Allison et al., 1963; Uttal and Cook, 1964; Bergamini and Bergamasco, 1967). According to the dual

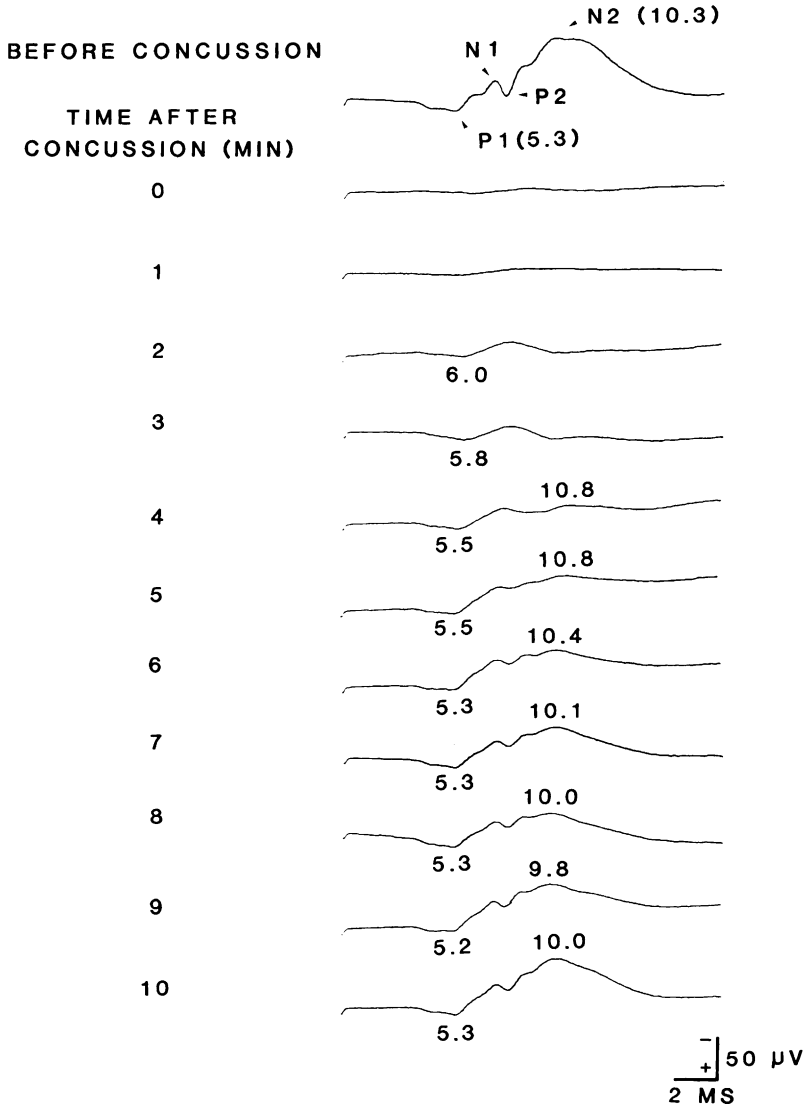

Fig. 1. The first of three examples of the effects of experimental concussion on the cortical somatosensory evoked potential (SEP) in the rat. Each set of data is derived from a single animal. SEPs were recorded over the contralateral somatosensory cortex following unilateral forepaw stimulation. The baseline SEP was recorded just prior to the concussive blow being inflicted. Subsequent SEPs were recorded at the times indicated after concussion. In the baseline (before concussion) SEP, the four principal components of the waveform are identified with the actual latency of the P1 and N2 components in parentheses. P1 represents the primary cortical response. In the following SEP traces, only the latency values of P1 and the late negativity (N2) are indicated.

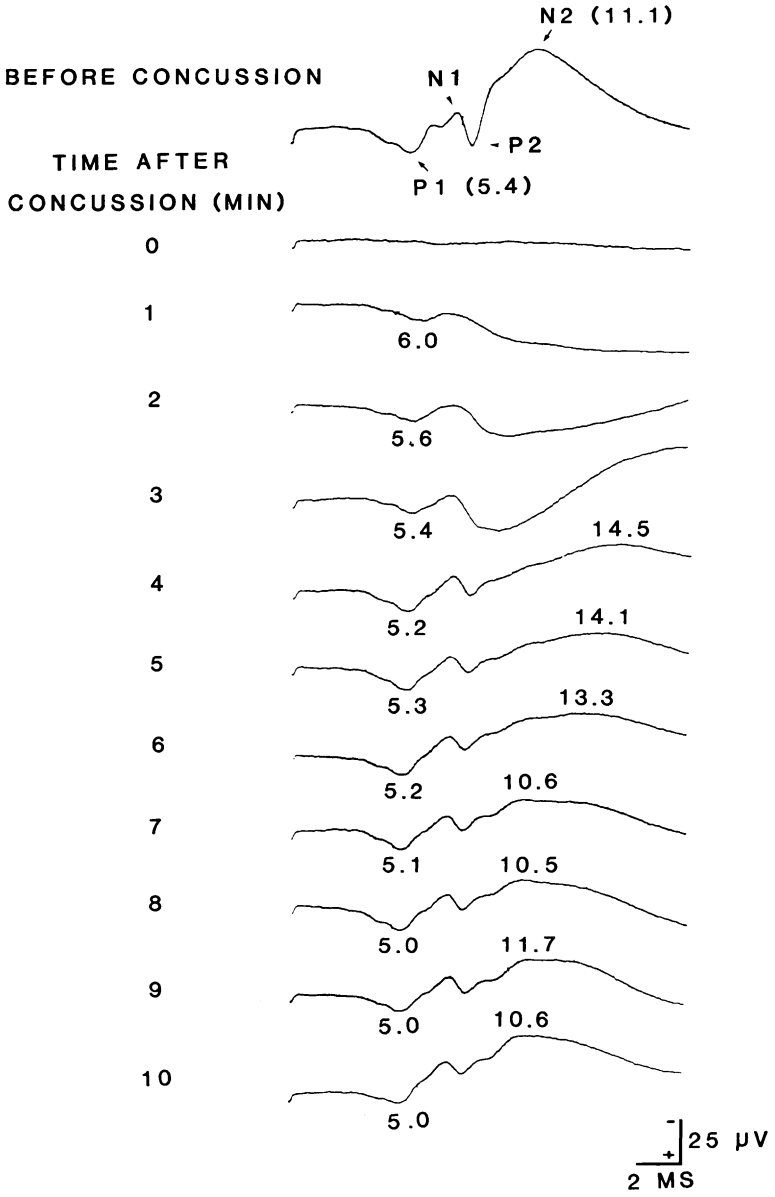

Fig. 2. A second example of the effects of experimental concussion on the rat's cortical SEP.

projection hypothesis, activity in the specific sensory pathways is responsible for the short-latency cortical responses while longer-latency potentials are mediated by non-specific reticular activity transmitted via distinct but parallel pathways (Williamson et al., 1970). The belief that a late cortical response such as N2 is a measure of activity in the ARAS would at least be consistent with the observation that under barbiturate anesthesia, the early components of the cortical SEP are preserved while the late ones are abolished or suppressed, e.g. Abrahamian et al., 1963; Rosner et al., 1963; Allison et al., 1963; Clark and Rosner, 1973; Shaw and Cant, 1981). It would also be congruent with the post-concussion SEP findings outlined above where recovery of wakefulness (judging by the return of the righting reflex) correlated closely with the restoration of component N2, albeit in a depressed state. Be that as it may, the notion that N2 is a sensitive indicator of ARAS function remains a theory with only tenuous circumstantial evidence in favor of it. A series of clinico-pathological studies later on in the 1960s provided not a skerrick of support for the dual pathway theory (e.g. Domino et al., 1965; Liberson, 1966; Stohr and Goldring, 1969; Williamson et al., 1970). It can be concluded from such studies that all components of the cortical SEP are most likely ultimately generated by activity traversing the specific lemniscal or spinothalamic tracts. Late responses most probably simply reflect delayed intracortical and interhemispheric processing of specific somesthetic information. It should also be considered that, as with the squirrel monkey data, not only middle and later components but also the early components of the

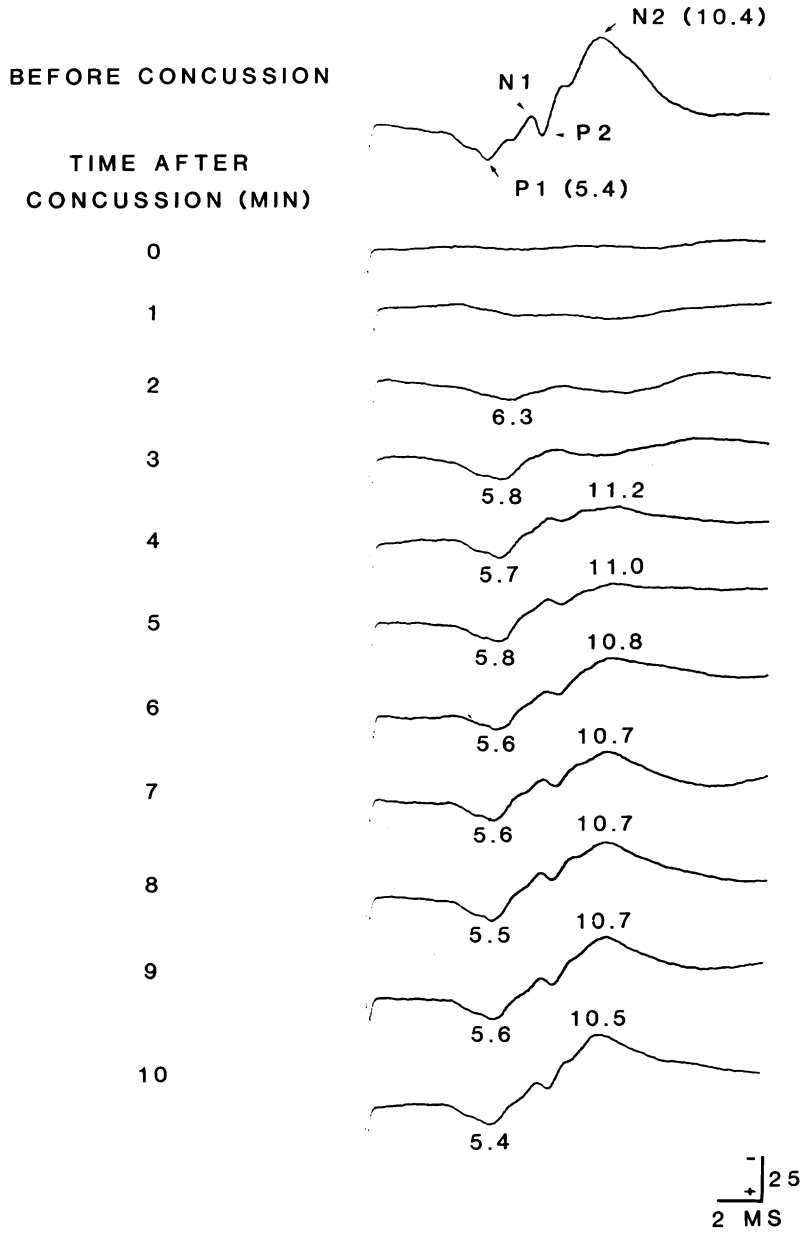

Fig. 3. A third example of the effects of experimental concussion on the rat's cortical SEP.

cortical SEP in the rat were simultaneously abolished by the concussive blow. As there is otherwise no compelling reason to suppose that the ARAS contributes anything tangible to the generation of the cortical SEP waveform, the rodent SEP findings can therefore provide no more indication of ARAS involvement in the pathophysiology of concussion than the comparable neurophysiological studies in primates.

4.2.3. Evoked potentials and compressive concussion

In addition to the experiments discussed above using acceleration concussion, there have also been a small number of studies examining the effects of fluid percussive injury on a variety of EPs. Some of these have been summarized further.

Katayama et al. (1985a) recorded cortical SEPs following dorsal root stimulation in the cat. Because of the number of responses which were required to be averaged to obtain a satisfactory response, the first SEP was not completed until about 3 min after the concussion. The cortical response obtained under these circumstances was grossly attenuated with an appearance not unlike the waveforms recorded by Shaw (1986a) at about 2–3 min post-concussion. Despite the limitations of the averaging procedure, the authors apparently ascertained that all components of the cortical SEP were initially extinguished following the concussive trauma. It would seem, therefore, that irrespective of whether concussion is induced by acceleration or compression, the cortical waveform is transiently lost during the acute period.

De Salles et al. (1987) recorded event-related auditory evoked potentials (AEPs) from cats. The potential studied was a late positive component homologous to the P300 potential recorded from humans and thought to be an electrophysiological correlate of the subject's attention to particular stimuli. First recordings began once the animal had adequately recovered from concussion judging by the return of reflex activity and spontaneous movements. This was 10–20 min after the head injury. Initially, the event-related AEP was completely lost but an earlier positive subcomponent of the waveform was re-established within 3 h of the head injury. In contrast, the slow long-latency positivity remained absent for at least 3 days and did not recover fully until 5 days after the concussion. The authors interpreted the relatively lengthy suppression of this complex AEP as a possible neurophysiological correlate of the cognitive deficits which may persist long after the concussion (Label, 1997). Regrettably, the nature of the event-related AEP, the uncertainty as to its electrogenesis and the conditions under which it can be obtained mean that such recordings can contribute little to the understanding of the acute pathophysiological processes which underpin concussion.

In the experiment by De Salles et al., brainstem AEPs (BAEPs) and early cortical AEPs had also been obtained at about the same time as the initial event-related AEP. The BAEP is a series of early high frequency wavelets arising mostly in the eighth nerve and the auditory brainstem (Hall, 1992). In a subsequent paper from the same laboratory, BAEPs were recorded from the anesthetized rat after the percussive blow and continued for the following 60 min (Lyeth et al., 1988a). Two groups of animals were employed. The first was simply concussed with the fluid percussion device but the second was treated with the anticholinergic agent scopolamine 15 min prior to trauma. Irrespective of whether the subjects had had scopolamine administered, the BAEP waveform was always preserved following percussive injury, albeit with a degraded morphology. Latencies were prolonged and later wavelets III and IV (poorly defined even in the baseline recordings) appeared to be missing for the first 2–3 min post-injury. Unfortunately, the authors provide just a single example of the effects of percussion concussion on the BAEP and virtually no group data. The finding that an antimuscarinic agent had no apparent effect on the BAEP following head injury is in contrast to behavioral data. The authors reported that periods of reflex suppression and other abnormalities were often significantly reduced in animals which had been given prior administration of scopolamine. With regards to the very ephemeral loss of BAEP components III and IV, it is uncertain to what extent this represents an interaction between concussion and the pentobarbital anesthesia. The later BAEP waves appear to be sensitive to even quite modest doses of barbiturates (Shapiro et al., 1984; Shaw, 1986b).

A rather more detailed description of the effects of concussion on the BAEP was later furnished by Shima and Marmarou (1991). They employed the anesthetized cat instead of the rat but a near identical fluid percussion injury technique. The device was calibrated so as to deliver high-level trauma. In retrospect, the subjects were divided into two groups on the basis of neuropathological findings. In approximately half of the animals, there was evidence of severe brain damage characterized by subarachnoid hemorrhage and widespread occurrence of petechial hemorrhages in the brainstem, midbrain and subcortex. In the second group, there was only mild subarachnoid hemorrhage and small scattered intraparenchymal hemorrhages in the brainstem and midbrain. It can probably be assumed that this latter group had suffered just a standard concussive injury. The first post-injury recording of the BAEP was made at 5 min and recordings then made at regular intervals until the end of the experiment at 8 h. The EP findings confirmed those of Lyeth et al. (1988a) that concussion may produce an overall reduction in the voltage of the BAEP waveform accompanied by an increase in the latency of all of its subcomponents but that it is otherwise not seriously altered by percussive injury. Even animals in the subgroup which had sustained severe brainstem damage still possessed a rudimentary waveform during the acute period. A major advantage of this study is that unlike most other reports of EPs and experimental head injury, the authors provide multiple illustrations plus a comprehensive statistical analysis.

While studies on the BAEP and concussion such as Lyeth et al. (1988a) and Shima and Marmarou (1991) are of interest, they are also of limited significance. This is because the first post-injury recordings of such activity appeared to be made at a time when the cortical waveform was also beginning to recover. The presence of a brainstem potential under such circumstances would therefore be hardly unexpected.

4.2.4. Evoked potentials and captive bolt stunning

Two methods are commonly employed to stun animals prior to slaughter in abattoirs. One is by the administration of electroconvulsive shock (ECS), a procedure which in this context is usually termed electrical stunning. The second is via a concussive blow delivered by a captive bolt. There are two variations of the captive bolt procedure: penetrative and non-penetrative. In the penetrative technique, the captive bolt is shot through the skull and lodges in the brain tissue. In contrast, the non-penetrative bolt has a mushroom-shaped head which strikes the skull but does not enter the brain. The latter technique is therefore very similar to the various kinds of impact acceleration which have been used in studies of experimental concussion. Despite the difference between the two versions of the captive bolt, both types can reliably stun an animal and are particularly used with cattle and to a lesser extent sheep. To further investigate its utility and mechanism of action, Gregory and co-workers at the Food Research Institute in Bristol conducted a series of experiments examining the effects of captive bolt stunning on EPs during the mid 1980s. All their studies employed the penetrative captive bolt.

Daly et al. (1986) recorded both cortical SEPs and flash visual EPs (FVEPs) from both ewes and wethers following captive bolt stunning in the standard frontal position. Most were anesthetized with halothane and nitrous oxide but some were concussed while awake. Irrespective of the state of consciousness, being shot with the captive bolt almost always resulted in an instantaneous loss of the cortical waveform. This remained absent for the remainder of the recording session which was approximately 5 min. The abolition of the visual and somatosensory responses is consistent with previous studies on the effects of experimental concussion on the cortical SEP (e.g. Ommaya and Gennarelli, 1974; Shaw, 1986a). However, it is uncertain whether the captive bolt inflicted a genuine concussive blow with just a brief loss of consciousness followed by a spontaneous recovery. Instead, it is more likely that what was delivered under these circumstances was a fatal blow, judging by the persistent absence of the waveform.

Somewhat different findings were obtained when the captive bolt was shot in the poll position (Daly and Whittington, 1986). Shooting in the poll position (i.e. over the back of the head or occiput) is mostly employed when the animal to be slaughtered is horned. Subjects for this experiment were anesthetized sheep and cortical FVEPs, but not SEPs, were recorded. The shot was delivered contralateral to the site of the recording electrodes. As in the previous experiment, the cortical waveform was lost immediately after the blow, but only temporarily in the majority of animals. Within 1 min, the FVEP had begun to re-emerge and by the end of the recording session at about 5 min, a near normal waveform had been regained. On the whole, such a pattern is similar to that previously described by Letcher et al. (1973), Ommaya and Gennarelli (1974) and Shaw (1986a). It appears that shooting in the poll position simulates concussion with survival much more reliably than in the standard frontal position, which in the context of the biomechanics of closed head injury may not be surprising.

In a subsequent study, the effects of captive bolt stunning on EPs were repeated using cattle (steers and cows) instead of sheep (Daly et al., 1987). Subjects were anesthetized (primarily with halothane), the captive bolt was shot in the standard frontal position and only cortical FVEPs were recorded. Findings were essentially the same as for the sheep studies, except that there was a marked variation among subjects in the brain's response to the concussive injury. In some animals, the FVEP was lost for the duration of the post-trauma recording period (6 min) as in Daly et al. (1986). In other subjects, the cortical waveform was absent for up to 1 min before beginning to recover in a manner similar to that described by Daly and Whittington (1986). For a third group, the FVEP was preserved although in a distorted and abnormal fashion presumably reflecting a state of being dazed rather than concussed. This type of heterogeneous response to an apparently standard injury is not unusual in the experimental concussion literature.

All three studies summarized above also recorded spontaneous cortical (EEG) activity. The authors make no comment on the presence or absence of epileptiform activity following captive bolt shooting. However, tonic immobility is an essential feature of a successful captive bolt stun. So, under normal circumstances, it would have been expected that excitatory activity would have been present in the acute post-traumatic EEG.

The significant of this group of experiments to veterinary practice and, in particular, to the humane slaughter of farm animals is beyond the scope of the present chapter (Eikelenboom, 1983). Still, with respect to its relevance to the pathophysiology of concussion, it does raise two difficulties both of which are explicitly addressed by the authors. First is the perennial problem of anesthesia contaminating interpretation of the EP findings in experimental concussion. In this respect, Daly et al. (1987) make the useful point that the extent to which concurrent anesthesia confounds such studies may be dependent upon what the physico-chemical basis of concussion actually turns out to be. Otherwise, in the present set of experiments, it seems likely that anesthesia did not seriously compromise the results. Where comparisons were made, there was not much difference between EPs recorded from animals concussed while awake and those which had been anesthetized. Likewise, there is a notable similarity between selected EP recordings among these studies and those made previously from a variety of animals concussed while awake.

The second problem relates to the use of the penetrative bolt to concuss the subject. It is important to disentangle any contribution of the bolt from that of the more general concussive impact to the loss or modification of the EP waveform (Daly and Whittington, 1986). In all three studies, autopsies were carried out on the brains of animals shot with the captive bolt. This was to ensure that the trajectory of the projectile did not target sensory pathways upon which the generation of the cortical EP was dependent. With an occasional exception, there was no evidence of any direct injury to these systems. In addition, unpublished observations by Gregory and Walton cited by Daly and Whittington (1986) are also relevant to this matter. They manually deposited a bolt through a hole in the skull in order to simulate tissue destruction which ordinarily accompanies firing of the bolt through the skull. No loss of the cortical waveform occurred as a consequence of this procedure. Taken into account with the post-mortem examinations, the authors concluded that it is the biomechanical forces set up by the velocity of the bolt striking the head which are principally responsible for the EP abnormalities, rather than any direct intracerebral damage.

In summary, the EP studies discussed above demonstrate that the cortical waveform is briefly but totally extinguished immediately after a concussive insult. Taken in association with the EEG findings, two principles regarding the acute neurophysiological findings following concussion can now be adduced with a fair degree of confidence. First, spontaneous cortical activity is characterized by an initial state

of hyperexcitability followed by a longer period of depression. Second, deliberately elicited cortical activity is lost, or at least fails to be generated. Any satisfactory theory of the pathogenesis of concussion must take into account and explain the significance of both the presence of the epileptiform activity and the simultaneous absence of the cortical EP.

5. Theories of concussion

5.1. The vascular hypothesis

The vascular hypothesis is the oldest of the formal attempts to explain the nature of concussion but little attention is now paid to it. The theory held sway for the best part of a century (Symonds, 1962) and Denny-Brown and Russell (1941) have traced its antecedents in the latter part of the 19th century. Probably its last major proponent was Scott (1940) whose studies of head trauma in the dog were summarized earlier (Section 2). The vascular theory endured for a lengthy period despite early experiments which should have discredited it at the time (Jefferson, 1944). This longevity might have been at least partly due to a lack of competing explanations.

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 and Russell, 1941; Walker et al., 1944; Symonds, 1962, 1974; Verjaal and Van '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. As Ward (1958) has observed, the membrane potential and therefore neuronal function can be preserved for sometime despite a cessation in its blood supply. This echoed the original criticism of Denny-Brown and Russell (1941). They argued that while alteration or disruptions in cerebrovascular function can theoretically account for loss of consciousness, reflex activity and other disturbances of concussion, they cannot explain their abrupt occurrence. Be that as it may, Ommaya et al. (1964) have subsequently suggested that cerebral ischemia might still be responsible for some of the side-effects of concussion including amnesia.

As Denny-Brown and Russell (1941) pointed out, among the most telling evidence against a role for vascular changes was actually reported in 1877 by Witkowski. In an ingenious experiment, Witkowski studied concussion in the heartless frog. A frog can be sustained physiologically and remain viable in this state for several minutes (Povlishock, 1995). An animal whose heart had been removed could be just as readily stunned as one which was intact. After a blow to the head, the frog would remain inert for several seconds before the return of spontaneous movements and the righting reflex (Denny-Brown and Russell, 1941). Witkowski's preparation therefore appeared to rule out significant vascular involvement in the genesis of concussion. In addition, much of the research reported by Denny-Brown and co-workers is also at variance with the vascular hypothesis. This includes data on venous outflow, ICP and the EEG (Denny-Brown and Russell, 1941; Williams and Denny-Brown, 1941).

A more recent rebuttal of the vascular theory arose from Nilsson's study of cerebral energy metabolism in the concussed rat (Nilsson and 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 and Ponten were able to demonstrate that a genuine concussive state could still be maintained in their animals without any marked exhaustion in energy reserves.

5.2. The reticular hypothesis

5.2.1. Introduction

By the middle of the 20th century, clinical observations plus experimental animal studies had ensured that both major and minor symptoms of concussion were well defined. On the whole, these seemed to implicate the brainstem as the principal site of action of concussion (Denny-Brown and Russell, 1941; Gordon and Ponten, 1976). Within the brainstem are located numerous nuclei and associated neuronal circuits concerned with the control of reflex activity and the maintenance of autonomic function. Consequently, the rise and fall of blood pressure, slowing of heart rate, the disturbances of CBF, the abolition of various reflexes especially the righting reflex which depends upon the integration of many brainstem nuclei, the loss of equilibrium, respiratory arrest, vomiting and nausea, muscle flaccidity and pupil dilation are all symptoms consistent with the theory that the trauma of concussion temporarily disrupts or disables brainstem function (Nilsson et al., 1977; Walton, 1977). The chief difficulty with such a principle is that it cannot readily deal with the cardinal feature of concussion which is the sudden loss of consciousness. In fact, it was not until well into the last century that there was a general acknowledgement that brainstem or subcortical mechanisms do play a crucial role in the control of level of consciousness (Brazier, 1980; Plum and Posner, 1980). Among the more persuasive evidence for this notion was the clinical and pathological data from patients who died from a form of encephalitis (encephalitis lethargica) during World War I (Brazier, 1980; Ottoson, 1983). This epidemic of what is commonly called sleeping sickness was characterized in the initial stages of

the illness by insomnia and in the later stages by lengthy periods of lethargy and sleep. When autopsies were conducted on these patients, wholesale destruction of neurons in certain areas of the brainstem was observed (Ottoson, 1983). Such findings suggested that a control center for sleep existed in the rostral brainstem. In 1944, Jefferson proposed that "traumatic stupor" might be produced by lesions of the brainstem and hypothalamus. However, it was not until the end of that decade when Magoun and co-workers began to explain the role of the BSRF in the modulation of wakefulness, that a cogent brainstem, or more specifically reticular, theory of concussion could be formulated.

5.2.2. The structural organization of the reticular formation

As described briefly in the section on EPs (Section 4.2.2) the BSRF is a small phylogenetically primitive core of neural tissue (Rose, 1952; Brodal, 1957; Lindsley, 1960; Magoun, 1963; Thompson, 1975; Hobson and Brazier, 1980; Plum and Posner, 1980; Brodal, 1981; Ottoson, 1983; Gilman and Newman, 1996; Butler and Hodos, 1996). It occupies a relatively ventral position and stretches from the top of the spinal cord to the rostral midbrain and ultimately extends into parts of the hypothalamus and thalamus. The BSRF is bound laterally by descending motor pathways and ascending sensory tracts. The medullary portion of the BSRF is sometimes referred to as the bulbar RF and the mesencephalic part as the tegmentum. The BSRF is composed of a mass of cell bodies, long fiber neurons and short interneurons intermixed and mingled to form a diffuse and complex net or reticulum. Such a polysynaptic undifferentiated network provides an optimum environment for the integration and analysis of neuronal activity. Some afferent pathways in the spinal cord conveying signals from muscles and skin feed directly into the BSRF. Nevertheless, most sensory inflow is received via collaterals which branch profusely off the specific sensory pathways. All sensory systems are thought to participate in this process with a notable contribution from spino-thalamic afferents. The organization of the BSRF is such that it facilitates the convergence and pooling of inputs arising from different sensory systems. The BSRF also contains many small specialized nuclei concerned with the control of motor and sensory function as well as the regulation of autonomic activities such as temperature, respiration, heart rate, blood pressure and metabolism.

The BSRF is anatomically and functionally linked to many subcortical structures particularly the subthalamus, the posterior hypothalamus and the medial, intralaminar and reticular nuclei of the thalamus. This latter group is often collectively labeled the non-specific or intrinsic thalamic nuclei. Multicellular reticulo-thalamic tracts terminate within some of these. The thalamic reticular nuclei possess widespread thalamo-cortical projections thereby providing a route for relaying and disseminating impulses between the BSRF and diffuse cortical locations (Rose, 1952; Hanbery et al., 1954).

5.2.3. Background to the discovery of the reticular activating system

While the function of the BSRF remained a matter of speculation until mid-century, its basic structure had long been established by classical neuroanatomists (Brodal, 1981). In a brief history of the BSRF, Thompson (1975) recounted that by the turn of the century, Ramon y Cajal had documented its extension, composition, appearance and connections with surrounding afferent and efferent systems of the brainstem. Further, Thompson also quotes Allen (1932) who surmised that the BSRF might be involved with the "inhibition, excitation and integration of brain activity." In retrospect, an astute supposition considering what was subsequently discovered about its functional role. There was also a much earlier intimation about the operation of the BSRF arising from the animal experiments of Adolph Beck who, it will be recalled, was a pioneer in the discovery of EPs (Stevens, 1973). Around 1890, Beck noticed that the cortical potential elicited by a light stimulus coincided with the immediate suppression or disappearance of the slow generalized spontaneous activity (EEG). It was some 60 years later before the significance of this cortical EEG arousal reaction was explained (Coenen et al., 1998).

Apart from anecdotal clinical accounts and the realization that the synchronization of the cortical EEG demanded a subcortical pacemaker, the first systematic attempt to understand the contribution of the brainstem to the maintenance or loss of consciousness was the experiments conducted by the Belgian neurologist Frederic Bremer. Bremer published a series of papers on this work, mostly in the latter half of the 1930s (Bremer, 1935a,b, 1936, 1937, 1938a,b, 1956). Subjects for these experiments were unanesthetised cats which had had a transection of the brainstem made at either rostral or caudal levels. Recordings of the EEG and observations of pupillary changes were made from the animals. In the so-called cerveau isolé preparation, the transection was made at mid-collicular level within the mesencephalon thereby isolating the brainstem from the cerebral hemispheres and eliminating the inflow of all sensory information except that of the olfactory and visual systems. Animals with this level of transection appeared to be in a state of permanent sleep or somnolence judging by their EEG which consisted of relatively high amplitude spindle-like activity. This was confirmed by ocular signs where the pupils appeared constricted and slit, a characteristic behavioral sign of normal sleep.

The second preparation was labeled encéphale isolé and the transection was made at the level of the gracile and cuneate nuclei thereby isolating the whole of the brain from the spinal cord. Sensory pathways concerned with the transmission of vestibular, trigeminal and auditory signals also remained intact under these conditions, i.e. all inputs from cranial nerves were preserved. Animals in this state displayed a near-normal sleep–wake cycle with periods of low voltage desynchronized EEG alternating with sleep activity. During the periods of wakefulness, pupils were dilated and showed other signs of alertness. Bremer interpreted this

data to mean that maintenance of wakefulness was dependent upon the cerebral cortex being energized by a cumulative inflow of sensory impulses from within the classical or specific afferent pathways. If this sensory influx drops below an optimum level, as apparently occurred with the cerveau isolé preparation, functional deafferentation of the cortex occurs and loss of consciousness, sleep, somnolence, coma or stupor ensues.

As Plum and Posner (1980) observed, Bremer's theory that wakefulness is dependent upon sensory activation of the cortex was more or less correct but a closer analysis of his data hints at a more complex model of the brainstem's role in the control of consciousness. For instance, in the encéphale isolé preparation, the sleep–waking cycle was normally maintained. This implies that even if Bremer's conception was basically right, it was still necessary to invoke some additional gating mechanism within the brainstem to regulate the flow of sensory information to the cortex. Likewise, Bremer could demonstrate with appropriately strong sensory stimulation, only a very weak and transient arousal pattern in the EEG of the cerveau isolé preparation which barely outlasted the stimulus. In contrast, when similar stimuli were applied during the sleep phase in the encéphale isolé preparation, a much longer lasting and more robust period of arousal (judged by the abrupt loss of sleep spindles and the appearance of low voltage high frequency EEG) could be sustained. This finding also intimated that some kind of non-specific arousal mechanism was operating within the brainstem but whose function had been disrupted by the cerveau isolé transection.

A further step in identifying the putative brainstem center capable of controlling consciousness was the discovery by Morison and Dempsey of the recruiting response (Dempsey and Morison, 1942; Morison and Dempsey, 1942, 1943). These investigators found that a discharge of oscillatory activity resembling sleep spindles in the cortical EEG of the cat was triggered following electrical stimulation of a site within the medial thalamus. Further, repetitive thalamic stimulation at about the same frequency (8–12 Hz) as spontaneous cortical spindling generated, at least initially, a rapid and progressive increase in the amplitude of the cortical potentials which then proceeded to wax and wane in voltage. This is what the authors defined as the recruiting response. As the recruiting waves could be recorded over widespread regions of the cortex, this indicated that thalamic pulses were being disseminated via slow conducting diffusely projecting thalamo-cortical pathways.

There is an impressive similarity between the recruiting response and various EEG patterns such as sleep spindles and to some extent the alpha rhythm with respect to their rate, waveform, synchrony and cortical distribution. This suggests that the medial nucleus of the thalamus houses a pacemaker which drives, synchronizes or otherwise regulates spontaneous electrocortical activity. Strictly speaking, the medial thalamus is not part of the BSRF but, as noted before, there are strong anatomical and functional connections. The demonstration of a non-specific mechanism located in the diencephalon, unrelated to any primary sensory relay pathway and concerned with the governance of arousal, therefore hinted that similar systems could be operating elsewhere in the brainstem (Plum and Posner, 1980). A more detailed description of the developments which led up to the discovery of the ARAS can be found in Brazier (1980).

5.2.4. The discovery and operation of the reticular activating system

The formal exploration of the arousal properties of the BSRF began in 1949 with a series of papers mostly by Magoun and co-workers (Moruzzi and Magoun, 1949; Lindsley et al., 1949, 1950; Starzl and Magoun, 1951; Starzl et al., 1951a,b; French and Magoun, 1952; French et al., 1952, 1953a,b; Segundo et al., 1955; French, 1957; Lindsley, 1960). Subjects were usually cats either anesthetized or in the encéphale isolé state. Stimulating electrodes were implanted in the rostral (mesencephalic) portion of the BSRF. In animals which were dormant or drowsy, delivery of high frequency impulses (100–300 Hz) to this structure produced an abrupt transition in electrocortical activity. Rhythmic high voltage low frequency potentials were transformed into a state of activation. This pattern consisted of generalized long-lasting desynchronized low voltage fast activity resembling that of an awake animal. This change in the EEG was similar to that achieved when the subject was normally aroused using natural sensory stimulation. Behavioral signs of wakefulness were also apparent following electrical stimulation in monkey as well as cat (French et al., 1952; Segundo et al., 1955). In addition, recruiting responses elicited by intrathalamic stimulation were abolished by simultaneous reticular stimulation. EP studies were subsequently able to demonstrate that information from all sensory modalities could innervate the BSRF but only in a gross undifferentiated manner (French et al., 1952, 1953a).

The discovery of such a non-specific alerting mechanism within the BSRF provided the missing link between the entry of an afferent signal into the brain with diffuse arousal of the cerebral hemispheres. As a consequence, Moruzzi and Magoun labeled this portion of the BSRF the ARAS. Plum and Posner (1980) have pointed out that ARAS is more appropriately considered a physiological system rather than an anatomical one, although the two terms BSRF and ARAS are sometimes used interchangeably. It soon became apparent that the ARAS could provide a more adequate explanation for the findings of Bremer. Accordingly, loss of consciousness was now considered to be due not so much to the deprivation or blockage of specific sensory stimulation but rather to a disruption or interference with the function of the ARAS possibly mediated via the non-specific medial thalamus.

In a complementary series of experiments, the effects of electrolytic lesions were separately examined on reticular and primary sensory systems in the brainstem and mid-

brain in both cats (Lindsley et al., 1949, 1950) and monkeys (French and Magoun, 1952). This was similar to the cerveau isolé preparation except that in Bremer's studies, both the specific and non-specific pathways had been severed in the same animal. Destruction of the central reticular core (with sparing of specific pathways) resulted in chronic unresponsiveness and continuous stupor. This was associated with slow synchronized EEG and spindling activity indicative of a sleeping or comatose state. As in the cerveau isolé preparation, no prolonged EEG arousal reaction could be elicited in such animals. In contrast, subjects who had lesions confined to the specific or direct sensory relay projections of the midbrain showed no interruption of normal sleep–waking patterns as judged by both their behavior and EEG. This set of experiments was crucial to the testing of Bremer's notion that the cortex is vitalized by specific sensory impulses. The findings were quite contrary to the predictions of such cortical deprivation. In summary, the lesion studies were consistent with those of the stimulation experiments and help confirm that the maintenance of wakefulness seems critically dependent upon the integrity and preservation of ARAS function.

Within a decade of the discovery of the role of the ARAS, a basic model of the physiology of consciousness had begun to emerge (Lindsley, 1960; Magoun, 1963; Hobson and Brazier, 1980). Briefly, sensory bombardment of the BSRF from the adjacent specific sensory tracts evokes wholesale firing within the multisynaptic reticular network. This state of excitation is transmitted either directly or indirectly to the cortex to induce generalized cortical and behavioral arousal. In particular, diffuse cortical stimulation seems to prime the brain for the arrival, perception and interpretation of afferent signals traveling via the classical pathways to specific sensory receiving areas. Cortico-fugal fibers, by which cortical impulses innervate the ARAS, help form feedback circuits and thereby assist in maintaining a constant tonic input from the ARAS to the cerebral hemispheres. Conversely, a loss of sensory driving due to disruption of ARAS activity would cause a reduction or failure of its activating properties and therefore a cessation of arousal signals conveyed to the cortex. This will result in an impairment of consciousness of varying seriousness (Plum and Posner, 1980). It was therefore concluded that the BSRF/ARAS in collaboration with the cortex and parts of the diencephalon play the cornerstone role in the regulation of sleeping and waking, alertness, attention and in the waxing and waning of level of consciousness, in general (Brodal, 1981).

Possibly the greatest challenge to this paradigm is disentangling the relationship between the ARAS and the diffuse thalamic nuclei. There is clearly a dynamic and synergistic connection between the two systems. The non-specific thalamic nuclei are sometimes considered to be just a subcomponent of the ARAS, hence its alternative title of the diffuse thalamic projection system (DTPS) (Lindsley, 1960). Judging by electrical stimulation, the DTPS may duplicate some, although not all, of the functions of the ARAS. However, the simplest conception of the relationship between the two systems is that of reciprocal control of cortical state (Magoun, 1963). The demonstration of the pacemaker properties of the DTPS suggests that this system exercises an essentially inhibitory influence on cortical activity (Yingling and Skinner, 1975). Thus, while activation of the ARAS ultimately generates a desynchronized arousal pattern in the cortical EEG, activation of the DTPS induces slower synchronized patterns such as sleep spindles, recruiting responses and possibly alpha rhythm. Level of arousal would consequently be dependent upon whatever system was currently dominant and therefore takes precedence over the other. How the two systems precisely interact to control EEG activity is still uncertain. Excitatory impulses arising within the ARAS might be transmitted more or less directly to the cortex via slow multicellular reticulo-thalamic and diffuse thalamo-cortical pathways and then simply swamp, override or otherwise demolish the existing slower rhythmic EEG. Alternately, ARAS activity might apply its effects more locally by suppressing or blocking the pacemaker operation of the DTPS (Plum and Posner, 1980). Trains of high amplitude rhythmic potentials would rapidly decompose or disintegrate and be replaced by a low voltage desynchronized arousal pattern in the cortical EEG. Contemporary understanding of how the thalamic pacemaking system normally works is summarized elsewhere (Steriade et al., 1990; Lopes da Silva, 1991; Steriade, 1995).

5.2.5. The reticular theory of concussion

The reticular theory has been the pre-eminent explanation for the pathophysiology of concussion for the best part of half a century (e.g. Foltz et al., 1953; Foltz and Schmidt, 1956; Chason et al., 1958; Ward, 1958; Friede, 1961; Ward, 1966; Brown et al., 1972; Martin, 1974; Walton, 1977; Povlishock et al., 1979; Plum and Posner, 1980; Levin et al., 1982; Smith, 1988; Ropper, 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 chief 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 BSRF/ARAS. According to the reticular theory, unconsciousness following concussion would therefore be mediated by much the same processes that produce somnolence, stupor or coma following a lack of sensory driving of the 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.

5.2.6. Neuropathological support for the reticular theory

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 and Schmidt (1956). This work was discussed in the EP section where it was pointed out that, at best, they provide only tenuous or equivocal support (Section 4.2.2).

There is also quite a large amount of neuropathological data which is at least compatible with the reticular theory (Plum and Posner, 1980). 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. Some representative examples of this type of research have been summarized further.

Windle et al. (1944) examined the presence of chromatolysis in brainstem neurons in the guinea pig after it was concussed by the same technique employed by Denny-Brown and Russell (1941). Chromatolysis indicates the disintegration or dissolution of the chromophil substance (Nissl bodies). Chromatolytic cell changes have long been used as an index of traumatic damage to neurons (Chason et al., 1958). While not apparent immediately after the head blow, such alterations in brainstem neurons were evident within 15 h and became progressively better defined within the next few days. Chromatolysis and loss of neurons were more prominent among the large ganglion cells of the BSRF than in other parts of the brainstem as well as in those of the vestibular and red nuclei. Similar findings were also observed following concussion in the monkey (Groat et al., 1945). Comparable results were subsequently reported by Gurdjian and co-workers (Chason et al., 1957) using a different (percussive) method of head injury in the dog. Although present throughout the brainstem, chromatolysis was most marked within the cells of the medullary portion of the BSRF. In contrast, Gurdjian (1972) found chromatolysis was more common within the upper brainstem following head trauma in the monkey. This small difference in the principal site of cellular pathology within the brainstem could have been due to the change in the animal subject but might just as well have been caused by the employment of impact acceleration in the later experiment. Friede (1961) also found evidence of chromatolysis within BSRF cells and elsewhere in the brainstem (e.g. vestibular nuclei) following acceleration concussion in the cat. Large cells were more prone to undergo chromatolytic alterations than smaller ones. As in the earlier work of Gurdjian, the medullary portion of the BSRF was more vulnerable than the pontine component. Later still, Brown et al. (1972) reported chromatolysis and other ultrastructural changes in the BSRF of a small number of guinea pigs. Chromatolysis was most noticeable in 10–15% of large BSRF neurons but was also present in intermediate and smaller sized reticular neurons.

Apart from such alterations in cellular structure, there is evidence of a substantial loss of neurons within the brainstem following experimental concussion (e.g. Groat and Simmons, 1950; Friede, 1961). This loss was observed 13 months after concussion in the guinea pig experiments and 8 days for the cats. Parenchymal hemorrhagic lesions may also occur at different levels within the brainstem following concussion using a variety of techniques (e.g. Schaller et al., 1941; Sullivan et al., 1976). Brainstem hemorrhage may be associated with damage of varying severity to nearby cells. Temporary but marked edematous and mitochondrial changes have also been observed in the medulla following impact acceleration in the rat (Bakay et al., 1977).

Povlishock et al. (1978, 1979) infused horseradish peroxidase (HRP) into the brains of cats mildly concussed with the fluid percussion device. Increased permeability to this protein tracer was used as an index of neuronal membrane damage. Widespread inundation with the HRP was observed in, and confined to, the neurons of the BSRF and associated raphé nuclei. However, the cellular flooding with the peroxidase tracer was quite transient. This implied that the traumatic injury delivered by the fluid percussion device produced just a slight temporary disturbance in membrane and metabolic function.

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.

Oppenheimer's clinical observations that limited primary axonal disruption may accompany even minor head injury were subsequently confirmed by a series of animal experiments, most notably the work of Povlishock and co-workers (e.g. Povlishock et al., 1983; Povlishock, 1986). They used their standard fluid percussion set up and the anesthetized cat as subject. Prior to concussion, HRP implants were inserted into the animal's brain. This was in order to anterogradely label a variety of cerebellar and cerebral motor pathways as well as to pinpoint and quantify reactive axonal damage. Impedance of axoplasmic transport provides a technique for detecting such traumatically-induced localized changes in pathway structure and function. Most of

the fibers labeled with the protein tracer passed through the brainstem which, as Povlishock argued, should be the most vulnerable site even following mild trauma. Shortly after head injury (within 1 h), evidence of intra-axonal peroxidase pooling could be detected within the brainstem efferents. Focal reactive swelling reflecting an accelerating build-up of axoplasm then became increasingly more severe. Eventually, the distal segment of the axon could become detached from its more proximal part. Evidence for this kind of progressive axonal damage could be found scattered throughout all the brainstem pathways studied including those associated with the BSRF. Still, individual fiber systems were not invariably affected. Also, the number of abnormal axons within a specific efferent pathway was only a very small percentage of the total.

Somewhat similar findings were concurrently reported by Jane et al. (1985) using non-impact acceleration injury to produce concussion in the monkey. By employing silver stain techniques, the authors were able to identify axonal degeneration in the medulla, pons and inferior colliculus 7 days after head trauma. Axonal damage was seemingly restricted to brainstem locations and was virtually absent from the subcortical white matter. The authors noted the congruity between the limited axonal brainstem damage sustained by their experimental animals and the neuropathological changes described by Oppenheimer (1968) in his deceased concussion patients.

The examples of the somatic and axonal damage outlined above are, at minimum, consistent with the notion that the substrate of concussion may reside within the brainstem. Be that as it may, they otherwise offer only circumstantial evidence in favor of the theory that concussion is underlain by a temporary malfunction of the ARAS. Moreover, with one or two possible exceptions, the neuropathological findings provide little insight into possible mechanisms of action. An enduring difficulty in this respect is that many of the structural changes typically do not become apparent until hours, days or weeks post-injury. Even then they may be only sparsely distributed throughout the brainstem, or elsewhere. They cannot, therefore, easily account for the acute symptoms although they could conceivably be involved in the more long-term sequelae of concussion (Povlishock et al., 1983).

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. For example, Friede (1961) attributed chromatolysis in the BSRF to reactive axonal changes following a lesion within the cervical spinal cord (maximal at C1 level) which interrupted many thick fibers. 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.

5.2.7. Putative mode of action of the reticular theory

Attempts to describe exactly how a concussive blow might instantaneously but temporarily paralyze BSRF function have been less than edifying. There is little unanimity over what such a disruptive process might entail. Nevertheless, even a superficial consideration of the biomechanics of acceleration concussion reveals how vulnerable brainstem structure and function could be to this type of insult. BSRF nuclei could be crushed, displaced, distorted or compressed by the rapid flexion or extension of the brainstem about the axis of the cervico-medullary junction. Alternately, sudden rotation of the cerebrum within the cranial vault may create shearing and tensile strains among the BSRF pathways. Widely used percussive methods of experimental head injury allow a type of compression concussion to be induced while the head is immobilized. If the reticular theory is correct, this would mean that the percussive blow must duplicate the forces acting on the brainstem of the freely moving head. It has been suggested that brainstem tissue is elastically distorted by the transmission of pressure transients in a manner thought to be similar to that of human closed head injury (Sullivan et al., 1976). Gurdjian and co-workers have argued that the mode of action of concussion is similar, irrespective of whether it is of the acceleration, deceleration or compression variety. In all three types, it is presumed that the loss of consciousness ensues because an abrupt rise in ICP generates shearing forces in the vicinity of the BSRF/ARAS.

With regards to the pathophysiological changes in the ARAS which might be triggered by a concussive blow, one of the most enduring theories involves a role for acetylcholine (ACh). It has long been reported that ACh may be abnormally abundant in the CSF following both clinical and experimental head injury (Bornstein, 1946; Tower and McEachern, 1948; Sachs, 1957). Accordingly, sudden deformation or compression of the brainstem might release copious amounts of ACh which flood the intercellular space and temporarily impede synaptic transmission within the ARAS. Ward (1958) has speculated that such a sequence might explain the apparent conduction block of sensory information within the ARAS reported by Foltz and Schmidt (1956). It could also account for why an anticholinergic agent such as atropine had beneficial therapeutic properties when

administered to comatose head injury patients (Ward, 1950). One of the difficulties with this explanation is that it is uncertain whether any sudden massive liberation of ACh actually is the cause, or is simply a by-product of the pathophysiological processes underlying concussion. It is also unclear whether the time frame for these events would be compatible with the immediate onset of the acute symptoms of concussion. The putative role of ACh in the mode of action of concussion will be discussed in more detail in the subsequent section on the pontine cholinergic theory (Section 5.4).

A somewhat different version of how a reticular theory might work was put forward by Friede (1961). According to this, rapid movement of the head about the neck would initiate stretching and flexion and consequently depolarization of nerve fibers in the region of the cranio-cervical junction. This would involve the discharge of large numbers of neurons within the cervical cord and not just the thicker fibers which remain permanently damaged and are ultimately responsible for the structural changes in BSRF cells. A wave of excitatory activity would sweep up the cervical spine and so destabilize the normal operations of the ARAS. As Friede pointed out, this sequence of events would explain not just loss of consciousness and reflex activity as well as breathing difficulties, but also the brief convulsive movements which were observed before animals became flaccid. It should be remembered that Friede's explanation is to some extent quite at odds with the more mainstream reticular theories which propose that the concussive episode is associated with a paralysis or depression of BSRF activity. In this respect, Friede's explanation may have more in common with Walker's convulsive hypothesis which will be subsequently reviewed (Section 5.5.2).

Severe head injury causing prolonged coma and residual disability is often assumed to be underlain by DAI (Strich, 1961; Clark, 1974; Ommaya and Gennarelli, 1974; Gennarelli et al., 1982a; Jane et al., 1985; Adams et al., 1989; Blumbergs et al., 1989; Dixon and Hayes, 1995; Povlishock, 1995; McIntosh et al., 1996). DAI is created by shearing and tensile forces associated with the head trauma which physically tear or snap the axons apart at the moment of impact. It has long been surmised that a milder version of such axonal strain might be the substrate for minor concussive injury (Strich, 1961; Adams et al., 1977; Blumbergs et al., 1994). Under such conditions, shearing strains and stresses would just stretch or distort the nerve fibers rather than actually rupturing or lesioning them. This should result in a sudden but ultimately reversible disturbance of pathway conduction. Activity propagated in projectional and associational tracts belonging to the BSRF and elsewhere should therefore be temporarily suspended. Povlishock and co-workers have indeed confirmed that neuronal tissue is not torn at the moment of impact following minor head injury. Otherwise, an axonal explanation does not seem especially promising for explaining the mechanism of action of a reticular theory of concussion. Povlishock has speculated (Povlishock et al., 1983; Povlishock and Coburn, 1989) that sudden stretching of long thick fiber tracts may generate focal points of interruption particularly at vulnerable brainstem levels. As discussed in Section 5.2.6 on the neuropathology, these precipitate progressively worsening reactive changes over time and may account for residual concussive symptoms. Nevertheless, an instant but transient paralysis of large numbers of nerve fibers traversing the BSRF would probably need to be demonstrated at the moment of impact in order for an axonal mode of injury to be feasible.

If the pathogenesis of concussion does not involve axonal alteration, it could entail somatic damage to brainstem neurons. Windle and co-workers believed that post-traumatic chromatolysis reflected direct mechanical damage to reticular and other brainstem cells. Such an assumption would be consistent with Denny-Brown and Russell's (1941) contention that a concussive injury brings about a paralysis of brainstem neuronal activity. The weakness of this general explanation was exposed by Friede (1961). He pointed out that it was difficult to account for why chromatolysis could be observed in only a few nuclei while leaving the majority unharmed. This was one of the reasons Friede developed the alternate theory that the primary site of action of concussion lay elsewhere than in the brainstem and that chromatolysis occurring within its neurons was, in fact, related to an axonal reaction. Subsequently, Povlishock provided evidence of what was described as subtle and reversible alterations in somatic function which were detectable immediately following a concussive injury (Povlishock et al., 1978, 1979). As discussed previously (Section 5.2.6), these involved the temporary flooding of reticular neurons with HRP. The authors inferred that such transient abnormalities might represent the pathophysiological concomitants of concussive processes, most particularly of the loss of consciousness. One of the more positive features of this data is that the timing of the cellular changes are rather more compatible with the actual concussive symptoms than in some competing explanations.

In summary, there is no definitive understanding over precisely how a concussive insult might induce a sudden temporary dysfunction within the ARAS. A number of possibilities, including some outlined above, have been proposed since the reticular theory was first mooted nearly 50 years ago. Unfortunately, no consensus exists among this somewhat heterogeneous collection and some of the modes of action proposed appear to be contradictory.

5.2.8. The descending reticular formation

There is one aspect of the reticular theory of concussion which is often overlooked even by its proponents (Govons et al., 1972). This is the fact that the BSRF exerts just as powerful an influence over descending pathways, spinal cord motoneurons and subsequent motor performance as it does over ascending tracts responsible for sensory inflow and concomitant arousal mechanisms (Matzke and Foltz, 1972). In fact, Magoun's earlier experiments on the role of the BSRF

were actually concerned with its motor rather than sensory properties (Magoun and Rhines, 1946; Rhines and Magoun, 1946). Electrical stimulation of the more caudal parts of the BSRF (especially the ventro-medial segment of the medulla) in cats and monkeys was found to have a mostly inhibitory influence on reflex activity and muscle tone. In contrast, stimulation of larger more rostral parts (in the pontomesencephalic tegmentum) had a generally facilitatory effect on motor activities.

The BSRF is closely connected both functionally and anatomically to the extrapyramidal motor system, so much so that it is sometimes considered to be formally a part of it. In any case, long reticulo-spinal tracts terminating on ventral horn cells represent the most important route by which cortical and subcortical components of the extrapyramidal system transmit their control to lower motor centers (Ruch et al., 1965; Everett, 1972; Smith, 1972; Thompson, 1975; Hobson and Brazier, 1980; Butler and Hodos, 1996). Irrespective of how the relationship between the two systems is conceived, both the BSRF and the extrapyramidal pathways seem to participate in the gross background activity underlying motor performance rather than in its precise execution. The neuromuscular control exerted by the BSRF seems to be principally mediated via the gamma efferent system involving gamma motoneurons and muscle spindles. Gamma motoneurons are under the regulatory control of excitatory and inhibitory impulses transmitted down the reticulo-spinal tracts from their respective sources in the BSRF. Activation of the facilitatory movement sites in the BSRF generates increased discharge of muscle spindles, while conversely, activation of inhibitory regions results in depression of spindle activity (Ottoson, 1983; Gilman and Newman, 1996; Baker, 1999).

The basic role of the muscle spindle is to provide the proprioceptive stimulation necessary to elicit the stretch reflex, most prominently in extensor muscles (Ruch et al., 1965; Everett, 1972; Kuffler and Nicholls, 1976; Floeter, 1999b). Briefly, stretching the muscle simultaneously stretches bundles of intrafusal fibers which compose the spindle and evokes firing of its primary sensory (annulospiral) receptors. Discharges in the spindle afferent pathways subsequently arc back to the sensory roots of the spinal cord where they monosynaptically connect with alpha motoneurons. Efferent impulses in these fibers terminate at muscle end-plates causing the extrafusal muscle fibers to contract and the efferent limb to stiffen or straighten. Contraction of the extensor muscles simultaneously initiates a lessening of tension on the intrafusal fibers and therefore a cessation of excitatory activity in the annulospiral receptors. Such stretch and associated reciprocal spinal reflexes play a crucial role in the maintenance of a standing position, in postural adjustments and in the co-ordination of righting and anti-gravity reflexes.

This is a very basic description of the neuromuscular processes underlying the stretch reflex and it is complemented by the operation of the gamma efferent system (Everett, 1972; Thompson, 1975; Ottoson, 1983; Floeter, 1999a). Spinal cord gamma motoneurons, reflecting the overall intrinsic inhibitory and excitatory control by the BSRF, more or less continuously stimulate the muscle spindles. This is achieved by innervating the polar regions of the intrafusal fibers causing them to contract and thereby stretch the central nucleated portion of the spindle organ resulting in an increased rate of discharge of the annulospiral receptors. The activity of the gamma system creates a self-regulating feedback circuit within the afferent and efferent loops of the stretch reflex. The resulting constant firing from the alpha motoneurons therefore directly and automatically maintains the extensor muscles in a partially contracted state. This enables sudden or rapid movements to be made with maximum efficiency and allows the primarily extensor muscles involved in the maintenance of posture and uprightness to remain in long-lasting semi-tonic state.

It is through this intrinsic excitatory inflow to the gamma system that the BSRF largely attains its goal of priming, integrating, co-ordinating and regulating the sensitivity of muscle tone and reflex activity and therefore increasing or decreasing the probability that a motor response will take place. It is in this role that the motor functions of the BSRF are most analogous to its ascending system. The original observations of Magoun and Rhines on the augmentation or inhibition of reflex activity can therefore be readily understood as due to a generalized modulating influence on spinal and muscle function rather than to a more direct activation of alpha motoneurons and contractile muscle fibers. If BSRF energization and facilitation of spinal motor mechanisms are abolished or interrupted, as in a spinal preparation or through sectioning of the BSRF, then muscles throughout the body become flaccid, tone is lost and reflexes become impossible to elicit (Matzke and Foltz, 1972).

It would be predicted that if concussive trauma does specifically target the BSRF, this should cause a sudden temporary cessation in not only its sensory but also its motor functions. In the descending system, such an impairment would deprive the gamma efferent system of its normal facilitatory innervation. This would set in motion a sequence of neuromuscular events which should leave a concussed patient lying in a supine position, with flaccid musculature and a paralysis of at least some reflexes. In addition, the BSRF also houses neural circuitry responsible for circulatory, respiratory, gastrointestinal and other autonomic activities. It appears that the BSRF exercises the same tonic control over these as it does over simpler spinal reflexes (Matzke and Foltz, 1972; Smith, 1972; Ottoson, 1983). In summary, it can be appreciated how the reticular theory can provide, at least superficially, a straightforward and elegant explanation not only for the loss of consciousness but also for the miscellaneous motor and autonomic symptoms which may occur following concussion.

5.2.9. Limitations of the reticular theory

Even a relatively cursory examination of the evidence purportedly supporting the reticular theory reveals that it is

built on quite flimsy foundations. Outlined further are seven shortcomings or flaws of varying seriousness.

1. Among the most widely cited data in support of the reticular theory are the EP findings, particularly those of Foltz and Schmidt (1956). The difficulties inherent in this and related work were analyzed in the earlier section on EPs and concussion (Section 4.2.2). To be fair, none of the EP studies discussed earlier can be used to refute the reticular theory. Equally, none of them can provide substantial or credible evidence in favor of it.
2. If the EP findings cannot be used to directly rebut the reticular theory, the same cannot be said of the EEG data recorded following experimental concussion. It will be recalled from the discussion of the dynamics of the operation of the ARAS (Section 5.2.4), that this system normally exercises a kind of inhibitory control over the pacemaker functions of the medial thalamus. However, if the ARAS relinquishes its usual restraint due to loss of activation, damage or other dysfunction, then the medial thalamic nuclei are free to resume their role of co-ordinating and synchronizing slower high amplitude cortical rhythms. It follows, therefore, that if a concussive injury temporarily incapacitates the ARAS, then the EEG recorded from the cortex would predictably be of a relatively low frequency high voltage type. In the earlier discussion on the effects of experimental concussion on the EEG (Section 4.1.3), it was concluded that in almost all instances, acute spontaneous cortical activity could be reasonably tidily classified into one of two quite contrasting patterns. The first involved an attenuation in voltage often with an almost total suppression of the EEG. The second involved a brief period of excitation often consisting of both high frequency and higher amplitude activity. The genesis of these two conflicting patterns remains a matter of dispute, but for the present purposes it is notable that neither is compatible with the predictions of the reticular theory. On not a single occasion was a sleep-like EEG reminiscent of a relaxation of ARAS control obtained in these studies. It is difficult to reconcile the near universal failure to observe the predicted EEG pattern with the theory that concussion involves depression of reticular activity.

   The disparity between the EEG findings and the predictions of the reticular theory have, in fact, been directly addressed by Hayes et al. (1988). It will be recalled from the EEG section that, following fluid percussion injury, a brief period of high frequency excitatory activity was recorded from the cat in this study (Section 4.1.3) No evidence of slow rhythmical activity could be found. In contrast, when radio frequency lesions were made in the rostral BSRF of the cat so as to transect the ARAS, lower frequency synchronized waves dominated the recording, as would be expected. The authors concluded that short-term traumatic coma was unlikely to be related to impairment or depression of the normal arousal properties of the ARAS.
3. Depression of BSRF activity can account for muscle flaccidity and reflex paralysis which follow cerebral concussion. But, it cannot cope with the initial convulsive movements which are a feature of so many animal models of concussion as well as anecdotal reports in clinical concussion. Under such conditions, an acute increase rather than decrease in BSRF activity would be expected.
4. Traumatic memory loss is among the most important signs of concussion. Symonds (1962), not an enthusiast, has remarked that the reticular theory struggles to cope with any form of traumatic amnesia.
5. Unlike the physiological data provided by the EP recordings, the neuropathological studies do at least offer more direct support for a reticular site of action of concussion. Nonetheless, at best, much of this is selective, circumstantial or ambiguous. Otherwise, any histopathological changes in pathways or nuclei of the BSRF provide only limited evidence that they could be specifically associated with the acute pathobiology of concussion.
6. Rather curiously for such a long-standing theory, there is nothing which approaches an authoritative understanding of exactly how a concussive insult could temporarily depress reticular function. A variety of neurochemical, neuropathological and neurophysiological mechanisms have been proposed but there is, as yet, no consensus as to which, if any, might be feasible. If the reticular theory was a genuinely robust one, it would seem incontrovertible that there should have been a better appreciation of its mechanism of action by now.
7. Finally, there is the more general question of whether loss of consciousness would necessarily ensue even if a concussive insult did manage to arrest or disrupt activity within the BSRF. The relationship between the maintenance or loss of consciousness and the operation of the ARAS is somewhat more complex than the model originally proposed. For example, there has long been a good deal of evidence that sleep–waking patterns may survive, or at least be re-established, following even quite extensive destruction of BSRF tissue (Milner, 1971). Normal periods of arousal were more likely to be preserved or recover following extirpation or destruction of the BSRF if the lesions were produced successively or if the animal was given prolonged intensive post-operative treatment or if particular methods were used to destroy or ablate the tissue (Adametz, 1959; Doty et al., 1959; Milner, 1971; Thompson, 1975).

Perhaps most noteworthy, Feldman and Waller (1962) conducted a series of experiments in the cat in which bilateral lesions were placed either in the BSRF or posterior hypothalamus. With destruction of the ARAS in the midbrain, the cortical EEG was predominantly and predictably a slower semi-rhythmic high voltage pattern characteristic of a sleep-like state. Paradoxically, the animal remained in

a reasonably attentive and responsive condition. Conversely, extensive lesions in the posterior hypothalamus resulted in a stuporous, comatose and unresponsive state. If the ARAS was then electrically stimulated or else receptor organs naturally stimulated, this produced a prolonged period of electrocortical activation (low voltage desynchronization). Nevertheless, such procedures had no influence on wakefulness and the animals remained somnolent and quiescent. These findings are consistent with even earlier drug studies using cholinergic agonists and antagonists which demonstrated that the behavioral and electrocortical components of arousal could be dissociated (Bradley, 1958). This was contrary to the original concept of the operation of the ARAS which assumed that the electrical and behavioral components of arousal were causally related (Lindsley, 1960). Feldman and Waller concluded that the ARAS in the BSRF might therefore be just responsible for the electrocortical component of arousal and wakefulness while a largely independent system operating in the hypothalamus controlled the behavioral components. This would be in accord with the report of Ranson (1939) who had originally demonstrated that destruction of this region of the hypothalamus was associated with a chronically somnolent state.

The significance of such investigations is that they seem to imply that gross levels of wakefulness or consciousness may be maintained even in the absence of intact ARAS function. In addition, there are clinical reports which seem to indicate that severe damage to the BSRF is not incompatible with a considerable degree of responsiveness by the patient (Lhermitte et al., 1963). Extrapolation of the research discussed above to the pathogenesis of concussion must obviously be done with caution. Nonetheless, at the least, it must cast doubt on the notion that a concussive insult somehow targeting BSRF tracts and nuclei would inevitably or necessarily result in a loss of consciousness and responsiveness.

In summary, if the reticular theory is to remain a viable and competitive explanation for concussion, it must be able to deal adequately with the challenges, the dearth of information and the discrepancies highlighted above. If it cannot, it is difficult to understand how it can be sustained. Some additional weaknesses of the reticular hypothesis were identified by Hayes et al. (1988).

5.3. *The centripetal hypothesis*

5.3.1. *Introduction*

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 and Gennarelli, who outlined their theory in a series of papers published in the mid 1970s (Ommaya and 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, 1966; Ommaya and 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 and 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 (Section 4.2.2) 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 and 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 and 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 and 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 and 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.

5.3.2. Evidence for the centripetal theory

Ommaya and Gennarelli assembled a somewhat diverse collection of data of varying persuasiveness in support of their theory. This included clinical, neuropsychological, biomechanical, pathological and physiological evidence. The clinical data, for example, relies on the common observation that various faculties recover in a sequential manner which is usually invariant irrespective of the time frame. Return of gross awareness precedes motor and sensory function which, in turn, is regained before cognitive and memory proficiency. It is argued that such a sequence is consistent with the centripetal theory because it reflects the relative susceptibility to accelerative trauma of the cerebral zones controlling these different functions.

Other clinical evidence was subsequently presented by Plum and Posner (1980). They observed how patients who survived major head injury, but were left severely disabled or in a PVS, normally show evidence of extensive hemispheric injury. In contrast, there are few indications of primary brainstem damage in such patients which is compatible with the predictions of the centripetal theory that the brainstem is relatively immune to closed head injury. Similarly, Levin et al. (1988) used magnetic resonance imaging (MRI) to measure the depth of brain lesions in a large group of patients who had suffered different degrees of closed head injury. Depth of lesion correlated well with the extent and duration of loss of consciousness just as the centripetal theory would predict. This study by Levin et al. confirmed one conducted 2 years previously in which the ability of MRI to detect primary brain damage was compared to that of computed tomography (Jenkins et al., 1986). MRI found evidence of cortical lesions in almost all (nearly 90%) of the patients who had suffered either a mild or severe closed head injury. Lesser numbers, but still a majority, showed the presence of hemispheric white matter damage. Brainstem lesions were present in only one of the 50 subjects. Intracerebral lesions never occurred in the absence of cortical injury. On the whole, there was a reasonably clear-cut relationship between the depth of the brain at which abnormalities could be detected and duration of coma or unconsciousness, just as described by Levin et al. However, unlike the latter group, Jenkins et al. chose not to relate their findings to the centripetal theory despite them being almost perfectly in accord with its predictions.

Among the most widely cited data used to buttress the centripetal theory are clinical and experimental neuropathological changes occurring after head injury. In Ommaya and Gennarelli's (1974) study using squirrel monkeys as subjects, there was a strong relationship between rotatory acceleration trauma and the presence of diffuse symmetrical hemorrhagic lesions of various types. These were most commonly located on the surface of the brain or subcortically. Lesions within the brainstem were rare and were always associated with severe trauma and evidence of damage elsewhere. This pattern of distribution of lesions was not apparent in those animals which were not concussed following linear acceleration. These results are also consistent with the predictions of the centripetal theory that mechanical brain injury is associated with widespread shearing strains most prominent in the outer regions of the brain. Quite similar findings were described in a series of post-mortem studies by Adams and co-workers on patients who had sustained severe head injury (Mitchell and Adams, 1973; Adams et al., 1977). Primary brainstem lesions only ever occurred in conjunction with much more sidespread damage to the white matter of the cerebral hemispheres, never in isolation. As Adams et al. (1977) observed, such findings fit almost precisely the predictions of the centripetal theory concerning the relative vulnerability of brain regions to blunt head injury. While this appears to be so, it is useful to remember Povlishock et al.'s (1979) caution that data like this may be of only tangential value in understanding the pathogenesis of much milder head injury where the loss of consciousness is so transient.

It is also of interest that Ommaya and Gennarelli chose to virtually ignore what seems to be among the most

compelling evidence in favor of their theory. This is their neurophysiological recordings which were summarized in the earlier section on SEPs (Section 4.2.2). It will be recalled that following the concussive injury, the dominant P2 component of the cortical SEP was suddenly lost in the squirrel monkey. The authors interpreted this finding as evidence of a temporary disruption of function in the alerting system of the brainstem, i.e. in the ARAS. Nonetheless, what was not satisfactorily explained is why not just P2, but all of the components of the cortical waveform were lost following concussion. The complete abolition of the SEP might be far more simply accounted for by a gross generalized disturbance of cortical activity. Such an explanation would seem much more compatible with the tenets of the centripetal theory that the cortex is the most vulnerable site of accelerative trauma than the rather dubious interpretation proposed by Ommaya and Gennarelli.

5.3.3. Limitations of the centripetal theory

The problems inherent in the centripetal theory are easily appreciated. The principal difficulty lies in trying to reconcile a primary site of action or impact at the cortex with a mechanism of action responsible for the loss of consciousness buried deep within the brain. The centripetal theory appears to imply that only very severe head trauma capable of penetrating to the mesencephalon can interrupt ARAS activity and so result in an actual loss of consciousness. According to Ommaya and Gennarelli's model, mild concussive trauma disrupts activity solely in pathways near the surface of the brain. This may cause amnesia, disorientation and confusion but since the centripetal forces under these conditions extend no further inwards than the diencephalon, no loss of consciousness. Therefore, the centripetal theory may be able to account for the very common case where a person may be stunned, dazed or dinged but otherwise suffer no serious impairment in level of awareness. Likewise, the theory can also explain coma of long duration following a near fatal blow. The real dilemma for the centripetal theory is that it seems to deny the existence of a short-term period of neuronal paralysis, genuine loss of consciousness and unresponsiveness occurring after relatively mild accelerative/decelerative trauma. Yet this is the essence of an authentic full-blown concussive episode and the principal reason why its pathogenesis has remained so perplexing. Indeed, as Ommaya admitted in one of his earlier papers, the sudden loss of consciousness is the most striking aspect of concussion (Ommaya et al., 1964).

The contradictions inherent in the centripetal theory outlined above would seem to represent a major stumbling block for it, but there are also more minor difficulties. First, the theory boasts that it deals more directly with the problem of traumatic amnesia than some of its competitors (Ommaya et al., 1964). This is probably correct. The putative mode of action seems to involve a disconnection of the pathways linking the hypothalamus and temporal lobe with the diencephalon (Ommaya et al., 1973). It remains a moot point whether this would be considered an adequate or conventional explanation for short-term memory loss.

In contrast to amnesia, the centripetal theory makes no attempt to account for convulsive movements which may accompany the acute concussive period. In fact, there is no obvious reason why progressive decoupling of the cortex from lower levels should induce seizure activity. Ommaya and Gennarelli (1974) make no mention of whether any such phenomena were seen in the squirrel monkeys. Nonetheless, in an earlier report by Ommaya's team, clonic movements were reported in the chimpanzee (Ommaya et al., 1973).

Finally, basically the same type of disparity seems to arise when trying to account for the minor vegetative and autonomic symptoms of concussion as for the loss of consciousness. The centripetal theory would predict that shearing forces sufficiently powerful to interfere with the ARAS would simultaneously disturb BSRF autonomic function as well (Ommaya, 1985). The problem is that nausea, vomiting, headache, breathing difficulties, cardiovascular changes and the like may still accompany even mild closed head trauma. This is despite the shearing stresses and strains apparently being restricted in such cases to the more superficial layers of the brain and therefore presumably unable to disturb the relevant brainstem nuclei.

The enduring legacy of the centripetal theory probably lies in its refocusing of attention away from the brainstem and back to the cortex as the principal site of action of concussion. Unfortunately, in spite of its good intentions, the theory appears to be systemically weakened by its tendency to be procrustean. Too many of the characteristics of concussion must be stretched or chopped in order to conform to its dictates.

5.4. The pontine cholinergic system hypothesis

5.4.1. Introduction

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 (Sections 4.1.3 and 4.2.3). 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, (Section 5.2.7) 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 and 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).

5.4.2. Evidence for the pontine cholinergic theory

Although the proponents of the pontine cholinergic theory gathered a large amount of data in favor of it, only selected studies have been summarized further. In an initial experiment, mild concussive injury was shown to increase local cerebral glucose utilization rates in the dorsal pontine tegmentum of the cat (Hayes et al., 1984). This upsurge in glucose metabolism was not apparent in other midbrain sites studied, where metabolic activity actually decreased. The authors concluded that such findings implied that concussive processes were specifically linked to functional activation of the pontine tegmentum.

In an attempt to substantiate the hypothesis, the cholinergic agonist carbachol was micro-injected into the same brainstem regions of a large number of awake animals. Within a few minutes of carbachol administration, the subjects began displaying behavioral symptoms of concussion similar to those produced by the fluid percussion device. These included a loss of muscle tone and abolition of flexion, righting and placing reflexes. It was observed that the animals did not react to even powerful stimuli. Desynchronized cortical activity was present. Curiously, corneal and blink reflexes were reported to be relatively unharmed in contrast to the situation with brain injury where they were lost for up to 5 min. The behavioral suppression normally persisted for 30–90 min but could be reversed by administration of atropine. The carbachol data was considered to be consistent with that of glucose utilization in suggesting that pontine cholinergic activity may play an important role in mediating loss of consciousness following concussion. Similar findings were also reported by Katayama et al. (1984).

Shortly afterwards, it was demonstrated that suppression of motor and sensory functions in the spinal cord following concussion originated from specific sites within the brainstem and not from direct transmittal of mechanical stresses and strains from a distance (Katayama et al., 1985a,b; Hayes et al., 1989). Systematic transections at spinal, midpontine or collicular levels further revealed that processes operating in the medulla seemed to be responsible for the suppression of sensory activity within the spinal cord. In contrast, the abolition of motor components of concussion were controlled by inhibitory influences which descend from the more rostral pontomesencephalon. This is the same region which contains the so-called cholinoceptive pontine inhibitory area (Katayama et al., 1984).

If concussive injury specifically activates cholinergic neurons, it would be expected that the administration of a muscarinic cholinergic antagonist under optimum conditions would shorten the period of unconsciousness. This would be judged by the alleviation of the various behavioral symptoms of concussion. These predictions were tested by delivering an i.p. injection of scopolamine either 15 min prior to or 30 s after the concussive injury in the rat (Lyeth et al., 1988a). Subjects were then assessed for 60 min using eight simple neurological tests and the results were compared to those of saline controls. These were pinna and corneal reflexes, paw and tail flexion reflexes as well as head support, righting, escape and spontaneous locomotion responses. The findings more or less confirmed the predictions. With a 1.0 mg/kg dose of scopolamine prior to concussion, the suppression time of almost all of the behavioral indices was significantly reduced. This trend was also apparent for the group administered a 0.1 mg/kg dose although to a much lesser extent. Surprisingly, the weakest influence of the scopolamine was observed in the group administered the strongest dose (10 mg/kg). The authors argue that at higher doses, scopolamine may lose its muscarinic receptor specificity. With regards to the animals injected with scopolamine (1.0 mg/kg) post-injury, there was a consistent decrease in suppression time for all the responses tested but this was seldom significant. Injection of 1.0 mg/kg of scopolamine prior to trauma had more generalized protective properties because it also reduced mortality by about 50%. However, administration of scopolamine after injury made no difference to the mortality rate. The authors maintain that this effect on mortality is more likely to be mediated by the putative anti-convulsant properties of scopolamine rather than by interference with the operation of an inhibitory pontine system. Otherwise, the explanation for the relative failure of scopolamine to either reduce mortality or decrease the suppression time of the behavioral responses when administered immediately post-concussion is basically the same. There is not sufficient time for the

anti-muscarinic agent to successfully block the requisite excitatory cholinergic activity.

More direct evidence of a role for brainstem cholinergic pathways in the induction of concussion was obtained by Saija et al. (1988). They used ACh turnover in selected cholinergic and cholinoceptive regions within the brain as a measure of cholinergic neuronal activity in the rat following mild head injury. Samples of activity were made at 12 min, 4 and 24 h after head injury which corresponded to the acute, transitional and long-term phases of concussion. Cholinergic activity in the thalamus, amygdala, hippocampus and cortex sometimes showed small increases or decreases or else remained unchanged. Still, only in the dorsal pontine tegmentum was there a marked increase in cholinergic neuronal activity, thereby appearing to strengthen the relationship between this region and the pathogenesis of concussion. The finding of increased cholinergic activity in selected brain sites is consistent with the numerous reports of increased levels of ACh in the CSF of experimental animals and head injury patients.

It is not just the acute loss of reflex and other activity after concussion which seems amenable to anti-cholinergic treatment. Lyeth et al. (1988b) examined the effects of scopolamine on more subtle behavioral deficits which may persist for a week after head injury. These are thought to be analogous to the clinical symptoms of the post-concussion syndrome and therefore may possess a similar etiology. Two kinds of behavioral performance were measured both before and then at regular intervals after concussion. These were beam balancing to assess vestibulomotor function and beam walking to evaluate motor co-ordination. The contingencies under which scopolamine was administered were identical to those of Lyeth et al.'s (1988a) previous experiment and near identical effects were obtained whether dealing with either short-term or long-term behavioral deficits. A 1.0 mg/kg dose of scopolamine injected either before or after head trauma significantly improved the animals' performance on both tests as well as the time it took to return to baseline levels in comparison with baseline controls. In addition, the scopolamine appeared to reduce the effects of concussion on weight loss. The previous observations that the drug decreased mortality rate were also confirmed. These findings were interpreted as evidence that muscarinic cholinergic processes may be involved in long-term neurological and behavioral disorders as well as the acute loss of consciousness. In other respects, the mechanism of action was thought to be quite different.

If cholinergic mechanisms are involved in the mediation of both short-term and long-term symptoms of concussion, then the question arises as to what is the chain of events which link them to the concussive blow. These matters are briefly mentioned in some of the papers discussed above but the issue is more directly addressed in a review article by Hayes et al. (1989). In this regard, the crucial assumption is that the period immediately following the head injury is characterized by neuronal excitation with its concomitant mass depolarization and subsequent release of excitatory neurotransmitters including ACh. This is the most likely explanation for the presence of large quantities of unbound ACh in the CSF of head trauma victims and experimental animals. Hayes et al. (1989) cite a variety of evidence from their laboratory and elsewhere in support of this contention, i.e. acute post-injury excitation. This includes evidence of muscle hypertonia, EEG changes, as well as increases in CBF, energy consumption and extracellular potassium. This and other evidence in favor of a period of acute neuronal excitation will be discussed in more detail in the following section on the convulsive theory of concussion (Section 5.5.4). It is also consistent with the conclusion from the EEG studies summarized in an earlier section that concussive insult generates widespread neuronal discharge immediately after the blow (Section 4.1.3).

ACh, as well as other neurotransmitters, can possess excitotoxic properties (Olney et al., 1983). According to Hayes' theory, prolific free ACh liberated as a result of head trauma may bind to diffuse cholinergic receptors producing a pathological level of neuronal excitation. This process may exacerbate injury already sustained by the cell by the mechanical stress associated with the head injury. Such an interaction might result in long-lasting or even permanent cellular damage and so account for the enduring or residual neurological and psychological disorders which comprise the post-concussion syndrome. Nevertheless, such an explanation is not directly relevant to the pathophysiology of the brief initial loss of consciousness following concussion and other acute symptoms. In this instance, it is envisaged that neuronal excitation specifically arouses the inhibitory system of the rostral pons. It is not especially clear whether this event also depends upon ACh binding to muscarinic receptors within this system. Alternately, activation of the pontine cholinergic system might be more directly triggered by depolarization of its neurons due to trauma-induced tissue deformation (Hayes et al., 1989).

5.4.3. Limitations of the pontine cholinergic system theory

As noted in the Section 5.4.1, both the pontine cholinergic and centripetal theories arose because of dissatisfaction with the reticular theory. It is of interest to compare how the different theories coped with the problem. The centripetal theory dealt with it by attempting to split the primary site of action from the mechanism of action. In doing so, one problem may have been solved but at the expense of creating a second. In contrast, the pontine cholinergic theory retained a site of action within the brainstem. However, a separate mode of action modulating level of consciousness was invoked obviously in very close spatial proximity to the ARAS of the BSRF. It is a moot point whether this represents an especially parsimonious solution.

Besides the studies of Hayes and co-workers (Hayes et al., 1984; Katayama et al., 1984), quite a number of investigators have conducted similar experiments (Hernandez-Peon

et al., 1963; George et al., 1964; Baxter, 1969; Mitler and Dement, 1974; Amatruda et al., 1975; Van Dongen et al., 1978; Van Dongen, 1980; Silberman et al., 1980; Velasco et al., 1981; Baghdoyan et al., 1984, 1987; Shiromani et al., 1986; Quattrochi et al., 1989). These mostly employed the cat as subject and carbachol as the cholinergic compound which was usually micro-injected into the pontine tegmentum or its precincts. Findings from such studies have on occasions been contentious or contradictory which have usually been attributed to differences in methodology or site of administration of the drug (Velasco et al., 1981; Baghdoyan et al., 1987). Nonetheless, on the whole they form a consensus that there exists within the pontine tegmentum a cholinergic system which, superficially at least, seems to be occupied with the generation of a paradoxical or rapid eye movement (REM) sleep-like state. This is judged electrically by the recording of a low voltage desynchronized cortical EEG and behaviorally by immobility, the loss of somatic reflexes and atonia of the postural muscles.

According to the pontine cholinergic theory, the pathophysiology of concussion also involves activation of this system. This implies that neural mechanisms governing the induction of REM sleep are the same or similar to those responsible for the loss of consciousness following concussive injury. There is now little doubt that ACh activity within the pons plays a key role in the induction of all components of REM sleep (Shiromani et al., 1987; Jones, 1991). Nevertheless, it is not at all certain whether activation of the pontine tegmentum in a manner conceived by Hayes and co-workers would necessarily even produce a loss of consciousness. While some have claimed that focal cholinergic stimulation does result in such a state (Hernandez-Peon et al., 1963; Amatruda et al., 1975; Silberman et al., 1980; Katayama et al., 1984; Baghdoyan et al., 1987), the problem remains that it is difficult to accurately assess level of arousal when the subject's responsiveness to external stimulation has been essentially paralyzed by generalized inhibition of motor functions and muscle hypotonia. Ocular responses and reflexes survive largely intact following infusion of carbachol into the pontine reticular formation. Careful examination of the unimpaired indices has led some experimenters to conclude that, despite appearances to the contrary, animals in this state were probably awake (George et al., 1964; Mitler and Dement, 1974; Van Dongen et al., 1978; Velasco et al., 1981). For example, cats blinked to threat, their eyes tracked moving objects and pupillary responses remained normal. In addition, REMs could apparently fail to accompany this state (Van Dongen et al., 1978) and the presence of a desynchronized EEG and other electrical correlates might just as readily be interpreted as evidence of alert wakefulness as of paradoxical sleep (Silberman et al., 1980). It is conceivable, therefore, that the true status of this pontine cholinergic inhibitory system might primarily be that of a system responsible for producing a cataplectic-like condition. This may or may not be normally involved in mediating the suppression of muscle tone and other motor components during REM sleep (Mitler and Dement, 1974; Van Dongen et al., 1978; Velasco et al., 1981). If this is the case, then the inhibitory control is assumed to be exercised via a reticulo-spinal pathway descending from the pontine tegmentum (Mitler and Dement, 1974; Velasco et al., 1981; Katayama et al., 1984; Morales et al., 1987). In summary, there is confusion and some doubt as to whether activation of the cells of the cholinoceptive/cholinergic inhibitory system within the pontine reticular formation is actually able to induce a state of sleep, coma or loss of sensibility. This would, at the least, tend to undermine its claims to be a likely or adequate model for the pathogenesis of concussion.

One key piece of evidence in favor of the pontine cholinergic theory has also been substantially weakened. In the experiment conducted by Hayes et al. (1984), evidence of increased glucose metabolic activity following concussive injury was confined to the pontine tegmentum. Surrounding areas almost invariably demonstrated a hypometabolic response. However, measurements in this study were not begun until 1 h post-injury. In a later study by some of the same authors, measurements of glucose utilization began immediately after head trauma in the rat (Yoshino et al., 1991). Although there was evidence of hypermetabolism within the brainstem, increased glucose utilization was far more prominent elsewhere in the brain, most notably in the cortex and hippocampus. This study will be further discussed in the following section on the convulsive theory (Section 5.5.4). For the present purposes, it seems to indicate that no unique relationship exists between an increase in glucose metabolism and the pontine tegmentum following a concussive blow.

Even if the suspicions outlined above concerning its capacity to generate a genuine state of unconsciousness are ignored, there still remains substantial difficulties with the pontine cholinergic theory. It will be recalled that pre-injury injections of scopolamine significantly shortened the suppression time of various behavioral indices of concussion (Lyeth et al., 1988a). Such findings are consistent with the notion that the induction of a concussive state is dependent upon cholinergic activity. Nevertheless, despite the administration of the cholinergic antagonist, a robust concussive episode invariably occurred judging by the abolition of reflex and other activity which persisted for several minutes. If the cholinergic inhibitory theory is correct, then it would have been predicted that blocking ACh receptor function should have completely protected the animal and prevented concussive injury from occurring at all. The authors are aware of this discrepancy. They attempt to circumvent it by invoking an initial unspecified disturbance of cerebral activity which springs into action even before the cholinergic processes (Lyeth et al., 1988a). It is therefore this nebulous generalized disruption of neuronal function which actually accounts for the immediate symptoms of concussion rather than the activation of the pontine inhibitory system. The problem with such a solution is that it seems to relegate this system to playing just a marginal role in the acute induction of concussion and in doing so

appears to weaken the pontine cholinergic hypothesis to near irrelevance.

Even any residual contribution to the acute symptoms of mild head injury need not necessarily be attributed to the possible operation of a specific mechanism residing within the pontine tegmentum. It is well documented from both clinical and animal studies that cholinomimetic and anticholinesterase drugs may possess analgesic properties (e.g. Pleuvry and Tobias, 1971; Dayton and Garrett, 1973; Houser, 1976). The ACh which is released following head trauma may be directly implicated in the pathophysiology of concussion or it may be merely a by-product of the mechanical injury. Irrespective of the role of ACh in the induction of concussion, it should nonetheless activate cholinergically-mediated pain inhibitory systems and pathways. It would therefore be predicted that there should be a post-injury period of antinociceptive activity which is relatively independent of any concussive phenomena. Moreover, this elevation in pain threshold should be countered or antagonized by muscarinic cholinergic receptor blocking agents such as atropine or scopolamine (Dayton and Garrett, 1973; Houser, 1976). An interaction between the prevailing level of analgesia and the degree of post-concussive behavioral suppression probably represents the simplest and most ready explanation for the findings of Lyeth et al. (1988a). This would be consistent with the observation that it was motor functions usually elicited by some form of noxious or aversive stimuli which were most susceptible to the pre-injury administration of scopolamine.

The interest of the proponents of the pontine cholinergic system theory appears to have waned in more recent times. In the previous section, it was suggested that the legacy of the centripetal theory may have been to shift the site of action of concussion to the cortex and away from the brainstem (Section 5.3). Similarly, the lasting value of the pontine cholinergic theory may be to have redrawn attention to the likelihood that the mechanism of action of concussion may initially involve a state of intense cerebral excitation rather than depressed neuronal activity.

5.5. *The convulsive hypothesis*

5.5.1. *Introduction*

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 and Posner, 1980). Likewise, the similarity between patients who have been concussed and those who have received electroconvulsive therapy (ECT) has often been noticed (Brown and 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 and Brown, 1954; Belenky and 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.

5.5.2. *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.

Brief details of the methodology employed by Walker et al. were described in the earlier section on the EEG (Section 4.1.3). As noted then, 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 described in the earlier section (Section 4.1.3). 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 and 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.

In retrospect, the paper by Walker et al. seems a rather unsatisfactory hybrid of an experimental article and a speculative review. The authors provide a great deal of detail about how the experiments were conducted but little actual information on the findings of such experiments. Almost always this consists of a sole figure illustrating a single subject. There is otherwise no systematic or group analysis of the results. This is despite the use of a very large number of subjects (for example 151 cats). It is also often difficult to determine which of the three methods was actually used to concuss the animal.

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.

5.5.3. The relationship between the symptoms of concussion and epilepsy

If the disturbance of cerebral activity following concussive trauma is of a similar nature to that which occurs during an epileptic attack, then it would be predicted that the symptoms of epilepsy and concussion should also be similar or even identical. Symonds (1974), not patently an advocate of the convulsive theory, has nonetheless written that "there is hardly any variant of post-epileptic disturbance of consciousness which may not sometimes be observed after head injury." It is therefore worthwhile to specifically compare the symptoms of concussion with those of a grand mal-type of generalized seizure. Both the major and minor symptoms of concussion and/or epilepsy have been frequently catalogued (e.g. Wright, 1951; White et al., 1961; Meyer et al., 1966; Holmes and Matthews, 1971; Kay et al., 1971; Merritt, 1973; Symonds, 1974; Muller, 1975; Verjaal and Van 'T Hooft, 1975; Schacter and Crovitz, 1977; Laidlaw and Richens, 1982; Marsden and Reynolds, 1982; Aird et al., 1984; Chusid, 1985; Lishman, 1988; Engel, 1989; Goldensohn et al., 1989; Smith et al., 1991; Bannister, 1992; Rosenthal, 1993; Nashef, 1996; Adams et al., 1997; Label, 1997).

Most obviously, both conditions exhibit a near instantaneous loss of consciousness which typically lasts for no more than a few minutes. The regaining of responsiveness and sentience may be almost as sudden as its loss but there may also then be a common period of drowsiness, stupor, disorientation, restlessness and lethargy of varying length. Both the epileptic and concussed patient initially falls to the ground and remains in a flaccid comatose state for at least part of this time. Withdrawal, stretch, corneal and other reflexes are normally depressed. Pupils are dilated and urinary and/or fecal incontinence may occur. Transitory respiratory arrest or apnea is nearly always seen. Blood pressure is usually reported to be initially increased in both epileptic patients and in animals undergoing experimental concussion. Likewise, there are alterations in heart rate in both epileptic patients and concussed animals. This is usually, but not invariably, reported to involve an acute slowing. Following both concussion and epilepsy, a variety of other disturbances in autonomic function are often reported. These include giddiness, nausea and vomiting. Complaints of post-ictal and post-traumatic headache are very common. In epileptic patients, tongue biting may occur if the tongue is caught between the teeth after convulsive spasms affecting the jaw. In concussed patients, laceration of the tongue is also not infrequent. In fact, injury to the tongue may be a principal reason why a concussed person eventually seeks medical attention.

Loss of memory for the events immediately preceding both an epileptic attack and a concussive episode usually occurs (retrograde amnesia). There is similarly little collection of events for a variable period following the recovery of consciousness for both the post-ictal and post-traumatic periods (anterograde amnesia).

It is not strictly fair to contrast the longer-term sequelae of a one-off concussive insult with that of chronic epilepsy. Nevertheless, it is useful to compare the similarity between the residual symptoms of the post-concussion syndrome with the personality and cognitive changes often attributed to epileptic patients in the interval between seizures. Common symptoms include irritability, depression, insomnia, inability to concentrate, anxiety, liability to fatigue, persisting headaches, restlessness, dizziness, temper tantrums, short attention span, impaired memory and learning, emotional lability, frustration, slowed mental processing and stressfulness.

Apart from the loss of consciousness, the most impressive feature of a grand mal-type of seizure is the presence of tonic and/or clonic convulsive spasms. As will be discussed in the next section on post-traumatic neuroexcitation (Section 5.5.4), many neurologists do acknowledge that similar excitatory motor activity may also occur immediately following a concussive blow but this is usually qualified by the statement that it is comparatively rare. In this respect, it was also previously argued that the occurrence of convulsive movements might be somewhat more frequent than supposed because they are usually missed or misinterpreted by naïve bystanders present at the time of the injury or accident. In addition, seizure activity occurring after concussion could be subclinical or electrographic without convulsive movements. Paroxysmal EEG discharges are frequently recorded from epileptic patients in the absence of any overt motor features. Also, convulsive movements after concussion appear to be much more conspicuous in animals with smaller sized heads and brains such as rats and cats than in primates (Walker, 1969). When motor excitation following concussive injury is detected in the latter, it may be more subtle such as the clonic twitching of facial muscles (e.g. rapid blinking of eyelids or flickering of eyebrows).

In summary, with the possible exception of convulsive motor activity, the clinical signs and symptoms of concussion are consistent with the notion that this type of craniocerebral trauma precipitates a state of neuronal excitation which closely resembles a generalized epileptic fit.

5.5.4. *Evidence for post-traumatic neuroexcitation*

Despite Walker's (1994) apparent second thoughts about the viability of the convulsive theory, a considerable amount of evidence has now been gathered in favor of an acute short-lasting period of intense post-traumatic neuronal excitation following at least a mild (concussive) type of closed head injury. The most direct and compelling evidence is, of course, the presence of convulsive activity, both motor and electrical. For more than a century there have been numerous reports that a wide variety of mammals may exhibit convulsive movements immediately following experimental concussion (e.g. Miles, 1892; Duret, 1920; Walker et al., 1944; Brown and Brown, 1954; Friede, 1961; Ommaya, 1966; Meyer et al., 1970; Govons et al., 1972; Ommaya et al., 1973; Nilsson et al., 1977; Huger and Patrick, 1979; Takahashi et al., 1981; Shaw, 1985a; Dixon et al., 1987; Ishige et al., 1987; Marmarou et al., 1994). Also convulsive-like twitching may be frequently noticed in birds which have been accidentally concussed after flying, for example, straight into a window (May et al., 1979). As noted previously, many authors do admit that such activity may on occasions also be detected immediately after clinical concussion (e.g. Walker, 1969; Merritt, 1973; Walton, 1977; Plum and Posner, 1980; Meldrum, 1982; Ropper, 1994; Adams et al., 1997). Because of technical limitations, there are not so many studies of spontaneous electrical activity recorded following experimental concussion. Nevertheless, when confounding factors such as timing of recordings and drugs are taken into account, there is nearly always an indication of high frequency cortical discharges resembling those seen in EEG convulsive activity (Section 4.1.3). Apart from these, there is also an increasing amount of physiological, neurochemical and metabolic research which is consistent with the excitatory hypothesis (Hovda, 1995) and a sample of this is summarized in Section 5.5.4.1.

5.5.4.1. Physiological and metabolic changes. Abundant studies have confirmed that increases in energy demand and utilization are characteristic responses of neurons to concussive trauma. For instance, Nilsson and Nordstrom (1977a) measured cerebral metabolic rate for oxygen during the first minutes following impact acceleration concussion in the rat. They reported an increase in oxygen consumption of the brain during this period which is consistent with the demands and occurrence of seizure discharges. The authors concluded that such findings of hypermetabolic activity lead credence to Walker's theory and are also in accord with previous experiments employing compressive injury such as Nelson et al. (1966) and Meyer et al. (1970). Nelson et al. struck the fixed head of the mouse with a sliding bolt. They reported an increase in cerebral metabolic rate for oxygen which occurred immediately after the brain injury. Likewise, Meyer et al. described an upsurge in oxygen consumption for the first 5 min following mild compressive trauma in the baboon. This increase in cerebral metabolism was accompanied in about half the subjects by evidence of excitatory activity in the EEG, as previously related (Section 4.1.3). In addition, both Nelson et al. (1966) and Nilsson and Ponten (1977) also reported an increase in the utilization of cerebral energy stores. This was indicated by a depletion in rich energy-containing metabolites such as adenosine triphosphate and phosphocreatine which began almost immediately after concussive injury.

In a later experiment, Duckrow et al. (1981) measured cortical oxidation of mitochondrial cytochromes as an index of oxygen sufficiency. Subjects were anesthetized cats concussed with the fluid percussion device. There was a short lasting increase in oxidative activity which peaked almost immediately or soon after the cerebral trauma in all the animals. Pre-injury oxidative levels were restored within 18 min. The authors interpreted these results as evidence

of an acute post-traumatic energy demand and conservation which was compatible with Walker's theory.

There have also been studies of increased glucose metabolic activity soon after concussion. As mentioned in the section on the pontine cholinergic system theory, Yoshino et al. (1991) measured local cerebral metabolic rates for glucose in the rat after fluid percussion injury (Section 5.4.3). These investigators provided evidence of a period of hypermetabolism which was apparent immediately after the concussive blow and persisted for at least 30 min post-injury. Although the rise in glucose consumption was apparent at a number of locations throughout the brain, it was most prominent within the cortex and hippocampus. The authors suggested that this rise in cerebral metabolism represented increased cellular energy demands needed to restore ionic membrane balance as a consequence of the period of mechanically induced neuroexcitation. In an earlier but less precise study, Shah and West (1983) had also found evidence of increased glucose metabolism following experimental concussion in the rat. However, the first measurements of glucose utilization were not made until 10 min after concussion. At this stage there was an indication of increased glucose uptake only at cortical level. Elsewhere, glucose consumption appeared to be slightly depressed. At 20 min, there was no evidence of hypermetabolic activity. Unlike Yoshino et al., concussion in this experiment was produced using an impact acceleration technique. This device was described earlier in Section 4.1.3 on EEG changes (West et al., 1982).

Increases in CBF may also be an index of abnormally heightened brain activity (Hayes et al., 1989). Such rises in CBF help meet the increased metabolic demands of the brain during the seizure and so maintain a near normal energy balance and adequate oxygen supply. De Witt et al. (1986) measured CBF in the cat using the radioactive microsphere technique following fluid percussion trauma. Minor concussive injury was associated with a small brief increase in CBF at 1 min which did not persist beyond 30 min. In contrast, more severe injury resulted in a much larger and more enduring rise in CBF which lasted for up to 1 h. These findings confirmed a number of previous studies of experimental trauma and cerebral hyperemia. For instance, Meyer et al. (1970) also described a limited rise in CBF following mild concussion in the baboon. Similarly, Nilsson and Nordstrom, 1977a) reported an initial rise followed by a more long-lasting fall in CBF after impact acceleration in the rat. Such results are consistent with the many studies which have demonstrated an acute increase in CBF occurring in both epileptic patients and experimentally convulsed animals (e.g. White et al., 1961; Meyer et al., 1966; Plum et al., 1968; Magnaes and Nornes, 1974; Meldrum, 1991).

5.5.4.2. Ionic shifts and neurotransmitter release. More direct evidence of diffuse neuronal excitation has arisen from attempts to detect depolarization of nerve cells soon after TBI. Most commonly, this has involved measuring ionic fluxes, especially extracellular potassium concentrations as well as the release of excitatory amino acid (EAA) neurotransmitters. For instance, Takahashi et al. (1981) inserted ion-sensitive microelectrodes into the brains of mice and rats almost immediately after the induction of concussion. Head trauma was produced by dropping a weight onto the fixed head. This procedure generated convulsive movements in many of the non-anesthetized control animals. Large increases in cortical potassium concentrations were found for both mice and rats which persisted for up to 30 min. Potassium concentrations were also measured from the rat brainstem where the increase in activity was more transitory and less pronounced. In a complementary experiment which did not specifically involve concussive trauma, Hubschmann and Kornhauser (1983) generated an experimental hemorrhage in the frontal subcortical white matter of the cat. A potassium sensitive microelectrode was implanted in undamaged cortical tissue adjacent to the hematoma. Judging by cortical field potentials, there was instant depolarization following induction of the intracerebral hemorrhage. This was associated with a sudden steep rise in extracellular potassium levels similar to that found for closed head injury in the rat.

The findings of Takahashi et al. and Hubschmann and Kornhauser were confirmed by Katayama et al. (1990) who provided a more complete description of the neurochemical events underlying the increase in extracellular potassium immediately following concussion. In this set of experiments, microdialysis techniques were employed to measure interstitial potassium concentrations in the hippocampus of the rat following either mild or moderate concussive injury using the fluid percussion device. In addition, selected groups had either tetrodotoxin (TTX) administered to inhibit depolarization, or else the calcium channel blocker cobalt to impede the release of EAA neurotransmitters. Mild concussive trauma resulted in a brief modest elevation in extracellular potassium which was largely prevented by the administration of TTX but not by cobalt. The authors interpreted these findings as evidence that the increase in extracellular potassium was more or less directly related to the depolarization of the neuron and its liberation was mediated via opening of voltage-gated potassium channels. Release of neurotransmitters was assumed to play no role in this process. In contrast, when the concussive force was greater, resulting in a lengthier loss of consciousness, there was a more marked and enduring increase in extracellular potassium. This was unaffected by the administration of TTX but modified by cobalt, implying a role for neurotransmitter release. It seems from such experiments that when extracellular potassium levels reach a critical threshold, they trigger further depolarization and the abrupt release of EAA (and other) neurotransmitters from nerve terminals, particularly glutamate. Post-synaptic EAA receptors subsequently activate the opening of their associated ligand-gated ion channels thereby permitting the rapid outflow of large amounts of potassium accompanied by a depletion (influx) of extracellular calcium (Nilsson et al., 1993). In other experiments, extracellular glutamate levels

were shown to briefly rise in parallel with those of potassium, thereby demonstrating that it was probably the release of EAA neurotransmitters which was responsible for the increase in potassium activity following the moderate concussive injury. This conclusion was reinforced by a final study involving the in situ administration of the EAA antagonist kynuremic acid which predictably dampened the increase in extracellular potassium.

In a concurrent experiment, Faden et al. (1989) also reported the release of EAAs following fluid percussion injury in the rat. On this occasion, microdialysis sampling was employed to measure extracellular accumulation of both aspartate and glutamate from regions within the hippocampus directly below the site of impact of the percussive blow. In contrast to Katayama et al. (1990), animals were subjected to either moderate or severe percussive injury and, predictably, the elevation in the level of EAAs was of much greater magnitude. This was especially so in the case of severe trauma. Concentrations peaked within 10 min of the blow but the increase in the interstitial concentrations of both aspartate and glutamate lingered for up to 60 min.

In a subsequent study, Palmer et al. (1993) measured extracellular levels of glutamate and aspartate following trauma utilizing the controlled impact model. This device employed a pneumatic piston to directly strike the exposed cortex (Dixon et al., 1991). Subjects were again rats but microdialysis probes were inserted in the frontal cortex rather than in the hippocampus. The findings that post-traumatic release of EAAs was dependent upon the extent of the injury are essentially the same as those reported by Katayama et al. (1990) and Faden et al. (1989) when using the fluid percussion technique. Still, extracellular concentrations of EAAs appeared to be much more pronounced following injury with the cortical impact device when compared with fluid percussion injury and they also remained elevated for longer periods, especially after a severe blow.

Nilsson et al. (1994) provided the most direct demonstration of the relationship between the release of EAAs following concussion and cerebral excitation. Brief details of this experiment are contained in Section 4.1.3 on EEG and concussion. It will be recalled that following head trauma in the rat, there was a period of intense epileptiform activity. Microdialysis sampling within the cortex also showed that there was a very substantial release of EAAs (glutamate and aspartate) and other amino acids following head injury which coincided with the seizure activity. Peak concentrations of the glutamate and aspartate occurred at about 4 min post-injury but had decreased to pre-injury levels within 10 min. This paper was a follow-up to a less specific study which had also employed the same weight drop cortical impact injury in the rat (Nilsson et al., 1990). As in their later experiment, the authors reported that extracellular concentrations of both aspartate and glutamate rose enormously but transiently after mild concussive trauma.

Finally, Globus et al. (1995) measured glutamate release following fluid percussive injury in the rat as part of an investigation into the effects of post-traumatic hypothermia. The authors reported an increase in extracellular glutamate levels which were maximal at the first sampling made at 10 min and remained elevated for the next 1.5 h. It was suggested that the extent of the glutamate release in this study was attenuated in comparison with previous ones because the microdialysis probe was inserted adjacent to the site of cortical impact rather than directly in it.

Experiments such as those of Faden et al. (1989), Katayama et al. (1990), Nilsson et al. (1990, 1994), Palmer et al. (1993), Globus et al. (1995) and many others have helped to provide the foundation of the so-called excitotoxic hypothesis (Regan and Choi, 1994; Smith and McIntosh, 1995; McIntosh et al., 1996; Novack et al., 1996). This posits that the release of toxic quantities of EAAs is at least partially responsible for the initiation of receptor-mediated secondary or delayed damage to neuronal tissue following a TBI of sufficient severity. This is thought to be largely due to a derangement in calcium homeostasis as a consequence of an excitation of EAA receptors activating associated ligand-gated ion channels (Tymianski and Tator, 1996). An abnormal accumulation of intracellular calcium sets up a chain of adverse biochemical events that lead to neuronal injury, degeneration and possibly death. Similar processes may be involved in the pathophysiology of cerebral ischemia or hypoxia, epilepsy and some neurodegenerative diseases. Be that as it may, for the present purposes the relevance of these studies is that the acute release of EAA neurotransmitters provides evidence of pathological neuroexcitation occurring immediately after head injury (Povlishock, 1995). Liberation of similarly large amounts of EAAs also accompanies spontaneous clinical seizures (Ronne-Engstrom et al., 1992). In addition, the many clinical and animal reports describing the abnormal release of large quantities of ACh as well as increased cholinergic activity following head injury also implicate massive and widespread depolarizing activity and possible excitotoxic effects (Bornstein, 1946; Hayes et al., 1989; Novack et al., 1996). Whether the release of EEA and ACh neurotransmitters dynamically contribute to neuronal excitation and firing or else are merely a by-product of extensive depolarization of the cell membrane remains controversial (Nilsson et al., 1994).

Reviewing this field more than 20 years ago, Shetter and Demakas (1979) considered that metabolic and physiological studies such as these summarized above provided the most cogent and persuasive data in favor of Walker's convulsive theory of concussion. This was before the nature of the post-concussive EEG had been clarified and before studies of ionic fluxes and excitatory neurotransmitter release had become available. Today, it seems incontrovertible that pure concussive trauma does trigger an acute short-lasting period of neuronal excitation and associated increase in cerebral energy demand. There are also experiments examining cerebral oxygen consumption, glucose utilization, oxidative metabolism, alterations in ionic concentrations and excitatory neurotransmitter release

employing epileptic patients or those receiving ECT as well as animal models of epilepsy (Meldrum, 1991; Adams et al., 1997). These are, of course, much more numerous than the type of TBI study presently described. Nevertheless, where comparable, essentially the same findings are almost invariably reported for both conditions. This strongly bolsters the argument that very similar cerebral hypermetabolic and excitatory disturbances underlie both epilepsy and concussion.

5.5.5. Traumatic induction of neuronal discharge

If the convulsive theory is correct, then the question must be asked as to what is the mechanism of action by which a concussive injury initiates widespread neuronal excitation. It will be recalled from Section 3 on biomechanics that four main forces have been identified which could participate in the pathogenesis of concussion. Three of these appear to conceive their final mode of action as interfering with or depressing brainstem function. However, the critique of the reticular theory has cast doubt on the extent to which the brainstem really is the principal site of action of concussive processes. The fourth biomechanical factor implicated in concussion was rotatory or angular acceleration of the head. It will be remembered from the discussion of the centripetal theory (Section 5.3) that Ommaya and Gennarelli (1974) have fairly persuasively shown that the rotational components of accelerative trauma are indeed the critical force in the induction of concussion. Ommaya and Gennarelli's experiment using non-impact inertial loading therefore helped to confirm Holbourn's original hypothesis that the principal site of action of concussion lies not deep within the brain but rather at or near its surface. Angular acceleration of the head will cause an abrupt swinging, swirling, shifting or spinning of the brain within the cranial cavity and therefore makes it likely to bump violently against the interior surface of the skull. Even if these collisions are not severe enough to inflict structural damage such as coup and contre-coup lesions, they are still liable to deform, indent or distort cortical tissue. Therefore, in any search to find the genesis of convulsive activity following a concussive insult, the sudden traumatic interaction between skull and cortex might seem the most promising candidate.

In fact, it has long been documented that mechanical stimulation of neural tissue can produce depolarization. For instance, Walker (1994) cites the studies of the 18th century physiologist Albrecht von Haller who in 1752 observed muscle contractions when an axon was tapped with a scalpel. Julian and Goldman (1962) quote similar findings from the work of Robert Tigerstedt in the late 19th century. As discussed earlier, (Section 5.2.1), Krems et al. (1942) blasted the exposed sciatic nerve of the frog using an air pistol in a procedure which was described as nerve concussion. A single blow could evoke a robust muscle twitch and repetitive discharges within the nerve fibers. Subsequently, Julian and Goldman (1962) reported that mechanical stimulation could cause depolarization and neuronal discharge of both the lobster giant axon and the frog sciatic nerve. The authors concluded that the breakdown of the membrane potential under these conditions might involve an initial direct compression of the axon followed by stretching and the physical derangement of the membrane. This allows increased permeability, ionic shifts and consequently the beginning of depolarization of the excitable membrane. Nilsson and Nordstrom (1977b) have argued that if the sequence of mechanical stimulation, deformation and increased membrane conductance of an isolated nerve fiber induces neuronal excitation and firing in this manner, then the same principles could presumably operate on a much larger scale following mechanical stimulation of cerebral tissue.

This conclusion would be consistent with the findings of Zimmerman and Putnam (1947) using the rat. They devised an electromechanical apparatus with which they could directly stimulate the exposed cortex with a vibratory force. When the animals were anesthetized with a standard dose of pentobarbital, the mechanical force typically produced a period of diminished EEG activity. In contrast, using the maximum traumatic stimulation in the very lightly anesthetized preparation could generate rhythmic epileptiform spiking in the EEG sometimes accompanied by convulsive movements. The authors noted the similarity between their findings and those of Walker et al. (1944).

More recently, Sachs and co-workers discovered the existence of widespread mechanosensitive ion channels in cell membranes which were not restricted to specialized mechanoreceptors (Morris, 1990; Sachs, 1991). Such channels are activated (or inactivated) by membrane stretch and related compressive and stressful forces. The demonstration of diffuse mechanosensitive ion channels thereby provides a more subtle mechanism by which mechanical trauma could increase membrane permeability and ionic flux. This means that it may not be necessary to invoke some type of damage or other physical alteration to the neuronal membrane, as originally envisaged by Julian and Goldman (1962) or Takahashi et al. (1981).

5.5.6. The paroxysmal depolarization shift and seizure generalization

With the mechanically-induced disturbance in ionic events, depolarizing sodium and calcium currents should begin to flow into the cell. As the depolarization proceeds, a positive feedback loop is established allowing for the opening of additional voltage-gated calcium channels, increased calcium influx and accumulation, and further depolarization. Once a critical threshold is reached, there should be an abrupt change in the membrane potential. This is known as the paroxysmal depolarization shift (PDS). The PDS is often considered to be the fundamental concept of how epileptogenesis is initiated and expressed at the cellular level (Prince, 1968; Matsumoto et al., 1969; Prince, 1978; Schwartzkroin and Wyler, 1980; Pedley and Goldensohn, 1981; Aird et al., 1984; Schwartzkroin and Wheal, 1984; Engel, 1989; Selzer and Dichter, 1992; Adams et al., 1997; Jefferys and Traub, 1998).

The PDS describes a large protracted high amplitude (30–40 mV) membrane depolarization which is sustained for at least 50–100 ms but may last much longer. Superimposed on the crest of the slow membrane potential is a continuous stream of high frequency action potentials. These repetitive epileptiform discharges are sometimes described as bursting. When a pool of such neurons simultaneously becomes hyper-excited in this manner, their summed and synchronized activity will be recorded in a surface EEG trace as a volley of epileptic spikes or sharp waves (Pedley and Goldensohn, 1981; Pincus and Tucker, 1985; Engel, 1989). However, once the PDS has become established, calcium-dependent outward potassium channels are activated (Hotson and Prince, 1980). This enables the efflux of potassium ions into the extracellular space and the initiation of inhibitory mechanisms to repolarize the cell. The inward calcium channels are closed, cutting off calcium conductance. The PDS begins to break up and terminates while the rate of firing of epileptiform discharges slows and then ceases. There follows a relatively lengthy period of hyperpolarization characterized by neuronal depression, electrical silence and a membrane potential significantly below that of the normal resting level.

It is not particularly clear whether there might be a role for excitatory neurotransmitter release in the sequence of traumatically-induced epileptogenesis outlined above. This could possibly involve depolarization of the membrane potential by EAA transmitters chemically activating inward ionic channels. If this is the case, it most likely involves the kind of positive feedback circuit described previously by Katayama et al. (1990) affecting potassium, calcium and sodium fluxes and the release of glutamate. EAAs have long been implicated in the pathogenesis of epilepsy and the induction of seizure activity in general (Olney, 1985; Meldrum, 1987). Moreover, EAA receptor antagonists possess powerful anti-convulsant properties.

Following a concussive blow, a population of synchronously discharging synaptically-coupled neurons should subsequently expand beyond its core sector of hyperactivity or epileptogenic focus. The spread, amplification and evolution of the seizure activity under these circumstances would presumably be mediated by the same mechanism as those which occur in a spontaneous epileptic attack of focal origin (Pedley and Goldensohn, 1981; Heinemann et al., 1996). The key role in this invasion of surrounding cortex is played by a pacemaker neuron (Wyler and Ward, 1980; Aird et al., 1984). Pacemaker cells swiftly recruit normal neurons into a state of synchronized excitation by bombarding them with trains of continuous epileptiform discharges arising from the PDS. Such enslaved cells may lie adjacent to the pacemaker or reside more remotely in synaptically-linked neurons. The pacemaker cells regulate the bursting activity and rhythmicity of the captured cells either through conventional chemical synapses or by electrotonic conduction via gap junctions (i.e. electrical collateral connections) (MacVicar and Dudek, 1981; Dudek et al., 1986; Dermietzel, 1998).

The above description is a rudimentary account of the possible cellular dynamics which could underlie the induction of a focal cortical source of epileptiform activity following a concussive blow. Irrespective of how accurate or relevant such a scenario might ultimately turn out to be, it is inevitably an oversimplification of a very complex sequence of neuronal events and interactions (Heinemann et al., 1996; Jefferys and Traub, 1998). In addition, a convulsive theory of concussion demands that such a local paroxysmal discharge must quickly expand to a more generalized state of seizure activity involving both hemispheres. How this is achieved is one of the most enduring problems in the study of epileptogenesis and the present article is not the appropriate place to rehearse the history of this often bitter controversy. For a contemporary perspective and review of these issues, it is useful to consult Meldrum (1988), Jasper (1991), Niedermeyer (1996) and Adams et al. (1997).

Three principal theories have been proposed by which a focal source of seizure activity can become secondarily generalized. All of them are variations of the more basic problem of the functional anatomy underlying primarily generalized seizures where the attack is apparently unlocalized from the start. First, there is the centrencephalon hypothesis put forward nearly half a century ago by Penfield and Jasper (1954). The centrencephalic integrating system is a hypothetical central regulating mechanism which to all intents and purposes is structurally and functionally equivalent to the ARAS (Meldrum, 1988). It can therefore be assumed to comprise the upper BSRF, its counterpart in the non-specific thalamic nuclei (reticular, midline and intralaminar) and the diffusely projecting thalamo-cortical afferents. According to the centrencephalic hypothesis, epileptiform discharges originating within the cortical focus would flood down cortico-fugal pathways to invade and activate the centrencephalon and its incorporated pacemaker mechanisms. The centrencephalon, in turn, would then transmit abnormal rhythmic impulses to the cortex thereby triggering a widely disseminated, bilaterally symmetrical and hypersynchronized state of seizure activity. This march of events would differ from that of generalized epilepsy only in so far that, in the latter case, paroxysmal activity must arise initially and spontaneously from within the centrencephalon as a consequence of an intrinsic disorder or dysfunction.

The legacy of the centrencephalic theory probably lies in its heuristic value as clinical evidence in its favor has remained mostly inferential. Possibly its most cogent support is derived from animal studies where functional pacemakers within the thalamus and reticular formation were repetitively electrically stimulated at low frequency. This technique has been found to elicit rhythmic cortical potentials in the EEG which superficially resemble generalized epileptiform discharges (Jasper and Droogleever-Fortuyn, 1947; Pollen et al., 1963; Weir, 1964). In contrast, intrathalamic recordings from epileptic patients have failed to detect paroxysmal activity in the centrencephalon occurring prior to the induction of a generalized cortical seizure (Meldrum,

1988). By coincidence, some of these recordings were obtained by Earl Walker who was the original proponent of the convulsive theory of concussion (e.g. Walker and Marshall, 1964; Niedermeyer et al., 1969).

Ajmone-Marsan (1965), amongst others, has challenged the need to invoke a separate comparatively remote non-cortical system such as the centrencephalon in order to account for the spread of seizure activity. Instead, the intrinsic rhythmic and self-synchronizing properties and connections of nerve cells, whether in a normal or abnormal state, should be sufficient to achieve this. This conception is commonly known as the cortico-cortical theory of seizure generalization and its chief advocate was Frederic Gibbs (Gibbs and Gibbs, 1952). Among the most widely cited evidence in support of a transcortical mechanism are a series of cat and monkey studies by Marcus and Watson where the preparations included ablation of the thalamus and sectioning of the corpus callosum (Marcus and Watson, 1964, 1966; Marcus et al., 1968). These used an experimental model of petit mal epilepsy and the findings were specifically at variance with the predictions of the centrencephalic hypothesis.

Such cortico-cortical events are basically just a perpetuation of the pathophysiological processes described previously whereby an epileptogenic focus progressively incorporates neighboring cells into a state of overactivity and hypersynchrony. Usually, such localized neuronal firing would be spatially and temporally contained by the operation of inhibitory interneurons and negative feedback circuits. This should create a band of inhibition enclosing the focus. Increases in the intensity of electrical discharges would breach this inhibitory surround sparking a chain reaction in which the convulsive activity would be spread rapidly and uncontrollably over the hemisphere as well as bilaterally presumably via callosal connections and other interhemispheric or subcortical pathways (Marcus and Watson, 1966; Marcus et al., 1968; Heinemann et al., 1996).

The third proposed mechanism of seizure generalization is the cortico-reticular theory. It was first formulated in the late 1960s by Pierre Gloor and is based, at least to some extent, on the feline penicillin model of primarily generalized epilepsy (Gloor, 1968, 1969, 1972, 1978, 1979, 1984). The cortico-reticular theory, as its name indicates, is a compromise between the intracortical and the centrencephalic mechanisms but is more subtle, elegant and complex than this may imply. For the cortico-reticular theory, a state of seizure generalization is dependent upon a dynamic interaction between both normal and abnormal activity in the cortex, non-specific thalamus and mesencephalic reticular formation. The crucial factor is considered to be the induction of a widespread level of moderately abnormal excitation in the cortex with a concomitant increase in neuronal responsiveness. Under such inherently epileptogenic circumstances, synchronizing thalamo-cortical impulses arriving at the cortex might act in a synergistic manner in order to trigger diffusely distributed epileptiform discharges. These subcortical volleys are generated within the thalamic pacemakers and are otherwise involved in the elicitation and synchronous phasing of standard cortical rhythms such as sleep spindles. This generation of generalized seizure activity (GSA) is, in turn, under the modulatory control of BSRF function. When ARAS activity is depressed, its desynchronizing influence on cortical rhythms is curtailed and seizure generalization is consequently enhanced (Gloor and Testa, 1974). The reverse, of course, also applies. The effects of the ARAS on cortical activity may be mediated either through direct connections or indirectly via lessening or tightening of its normal inhibitory grip on the diffuse thalamic nuclei. The mesencephalic branch of the BSRF and the non-specific thalamus therefore share basically the same reciprocal relationship with regard to the control of GSA as they do for natural cortical rhythms.

The theories outlined above illustrate three ways in which traumatically-induced seizure activity might be diffused throughout the cortex. For the present purposes, it does not matter which one or combination of these might ultimately turn out to be correct. The cortico-cortical hypothesis is the simplest and is therefore often assumed to be most likely correct. The centrencephalon theory has long been considered discredited although Niedermeyer (1996) has discerned a recent revival in interest. Intuitively, the cortico-reticular theory might seem the most reasonable, being a synthesis of the other two. In the present context, the difficulty is that the cortico-reticular theory is not at all explicit over exactly how it would account for an epileptogenic focus becoming secondarily generalized.

5.5.7. Traumatic depolarization and fluid percussion injury

The direct brain deformation model of TBI essentially consists of the rapid loading of the exposed intracranial contents (Anderson and Lighthall, 1995). There are two principal versions of this type of compression concussion: fluid percussion and cortical impact (Dixon and Hayes, 1995). The operation of these two techniques has been discussed elsewhere in this review (Sections 3.1 and 5.5.4.2). The fluid percussion injury device, in particular, has become the model of choice in lower mammals, not just for simple concussion, but for TBI in general. Much of the data discussed in the present article has been derived from the employment of this device and it is frequently remarked how well it can reproduce the symptoms of the more natural accelerative/decelerative-impact trauma.

In this context, it is notable that the biomechanical events associated with the application of a fluid pressure pulse or a mechanically-driven rigid piston to the intact dural surface would seem to share many of the same features as when the head is suddenly rotated and the brain impacts or dashes itself against the skull wall. Both traumatic procedures appear to entail an abrupt deformation, compression or distortion of the cortical tissue by mechanical stimulation. Under either condition, this should therefore initiate focal cortical depolarization.

If the convulsive theory is correct, then all models of experimental concussion must possess a common mode of ac-

tion which consists of generating an acute state of neuronal excitation. The explanation proposed above therefore seems to provide a means of reconciling the biomechanics of percussive concussion with the demands of the convulsive theory. Percussive devices are usually thought to exert their effects via rapid compressive forces eliciting ICP stresses and strains, especially within the brainstem (Lindgren and Rinder, 1969; Sullivan et al., 1976). These may be responsible for more severe types of experimental TBI, but the present interpretation suggests that they are not involved when dealing with a mild type of closed head injury like concussion.

Also, it will be recalled from the discussion on experimental concussion and the EEG that epileptiform activity was seemingly easier to obtain when employing a percussive type of device than with impact acceleration methods. This might seem incongruous considering that the latter clearly reproduces the biomechanics of standard clinical concussion rather more accurately than the former. This discrepancy could be resolved if it is accepted that deformation or compression of cortical tissue is the crucial factor in the induction of the GSA underlying a concussive state. It follows that this action is easily and directly achieved using a percussive injury device such as the fluid pulse or piston. In contrast, equivalent mechanical stimulation of the peripheral substance of the brain by impact with the skull bone would seem a much more cumbersome, indirect and unreliable method of similarly accomplishing this task. It is perhaps not surprising that seizure activity may be easier to induce and more prevalent when employing a percussive model even when the subject is concurrently anesthetized. A convulsive theory may also explain why the fluid percussion injury device is most efficacious when employing small mammals as subjects such as cat, rat or mouse. A single pressure pulse would obviously induce traumatic depolarization and subsequent propagation of a state of GSA more readily and completely when dealing with a brain of comparatively small size.

5.5.8. Post-traumatic loss of consciousness

Sudden temporary loss of awareness is the most characteristic and enigmatic symptom of concussion. According to Plum and 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.

Some insight into the pathophysiological mechanisms governing loss of consciousness following the induction of GSA can also be gained by recording EPs immediately after the administration of ECS (Shaw, 1985b, 1998a,b). In these studies, it has been reported that while the cortical waveform was invariably abolished, the thalamic EP (as well as more caudally generated EPs) were always preserved basically intact. These findings suggest that the induction of GSA does not prevent the afferent volley from penetrating deeply into the brain until it is finally and totally blocked at the cortical level. Such data are, of course, rather more consistent with cortico-cortical and cortico-reticular theories of unconsciousness than with the centrencephalic theory. This model is also reminiscent, to some extent, of the cerveau isolé preparation and Bremer's conception of the physiology of unconsciousness.

The disappearance of the cortical EP waveform is a reflection of cortical deafferentation and as such can be used as a neurophysiological correlate of unconsciousness. Still, it is not yet known how or why GSA can transiently destroy the cortical EP. A tentative explanation has recently been proposed (Shaw, 1998b). This stemmed from the discovery that calcium-mediated spikes (or after-potentials) arising within the dendrites seem to play a decisive role in the development of the PDS and neuronal burst firing patterns (Prince, 1978; Wong and Prince, 1978, 1979; Schwartzkroin and Prince, 1978; Schwartzkroin and Wyler, 1980). These dendritic potentials are generated in the same post-synaptic locations as the primary components of the EP waveform. It is possible that in the competition for generator space, the more dominant calcium spikes might just pervade the locations normally devoted to the creation of the cortical waveform and therefore thwart its formation. When the seizure begins to abate, the spiking activity attenuates and dendritic space becomes available again allowing the cortical waveform to re-emerge. There is no direct evidence to support this explanation nor is it entirely satisfactory but the notion that the cortical EP is passively prevented from being generated rather than being actively destroyed by the GSA is, at the least, parsimonious.

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 and Tucker, 1985; Engel, 1989).

The intense cerebral metabolic activity needed to sustain a generalized seizure will rapidly deplete energy stores. Neuronal exhaustion might therefore seem an obvious candidate to account for seizure termination. In the context of a convulsive theory of concussion, this seemed to be the mechanism favored by Walker and co-workers. Nonetheless, there has long been unanimity that, in the case of a transient seizure, termination is most likely to be due to an active inhibitory state (Efron, 1961) involving a number of mechanisms (Engel, 1989; Heinemann et al., 1996). Some of the basic ionic events involved in depolarization of the neuron were reviewed previously in the discussion on the PDS. In addition, release of the principal central nervous system inhibitory neurotransmitter γ-aminobutyric acid will activate channels permitting the inflow of chloride ions thereby facilitating a period of after-hyperpolarization and membrane stabilization. Further, an abnormal accumulation of extracellular potassium ions may eventually block cellular firing and therefore contribute to the overall post-ictal dampening of neuronal activity. Additional factors which might be involved in the cessation of convulsive activity have been summarized elsewhere (Aird et al., 1984; Engel, 1989; Selzer and Dichter, 1992; Heinemann et al., 1996). These include glial uptake of potassium ions and excitatory neurotransmitters, extracellular acidification as well as adenosine triphosphate and neuropeptide release.

Ultimately, ionic pumps will restore the membrane potential to its resting condition and a resumption of normal function. This should be the precursor to a relatively swift return of awareness and responsiveness following the brief period of unconsciousness. A convulsive theory can therefore simply account for the striking reversibility of the brief traumatic loss of consciousness which has long remained one of the most inexplicable characteristics of concussion.

5.5.9. 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 and 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 and 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 and 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 com-

mon 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.

Both concussion and GSA possess potent amnestic properties when dealing with a newly acquired memory. If the convulsive theory of concussion is correct, this obviously simplifies matters as both agents would interfere with short-term memory storage through a common mode of action. A viable theory of concussion must be able to account for traumatic amnesia as readily as it can explain the loss of consciousness (Ommaya et al., 1964). Many theories of concussion have been proposed in addition to the five discussed in the present review. It is an Achilles heel of nearly all of them that they either ignore, or else fail to cope satisfactorily with, the problem of traumatic amnesia. One of the great advantages of the convulsive theory is that it can deal more readily and adequately with the loss or impairment of recent short-term memory than almost any of its rivals. Rather curiously, this point is not generally emphasized even by those who favor the convulsive theory or who are sympathetic to it, but there are exceptions (e.g. Nilsson et al., 1977).

5.5.10. Post-traumatic convulsive movements

Related to the question of how a concussive blow may induce GSA is that of how it may concurrently produce convulsive tonic or clonic spasms of the muscles. This is despite the fact that convulsive motor activity may not be such a conspicuous facet of concussion as is loss of consciousness, at least for higher mammals. The mode of action of convulsive movements, as in spontaneous seizure disorders, would seem to implicate direct excitation of the descending motor centers of the BSRF by neuronal discharges originating in the cortex and subcortex (Aird et al., 1984; Fromm et al., 1987). These are likely to be propagated down the somatic motor pathways of both the pyramidal and extrapyramidal tracts. Despite their association with motor activity, these pathways have a combined catchment area which extends over virtually the entire cortex. The close functional and anatomical relationship between the extrapyramidal system and the BSRF has been previously emphasized. Although the pyramidal system chiefly terminates in the motoneurons of cranial and spinal nerves, it nonetheless has profuse collateral connections with BSRF. The development of convulsive movements may also be facilitated by the temporary loss of control by subcortical inhibitory centers (Aird et al., 1984).

In the earlier Section 5.2.8 on the operation of the descending BSRF it was explained how this system normally exercises a rhythmic tonic control over motor activity. It achieves this indirectly via stimulation of the gamma efferent system which principally comprises the gamma motoneurons and muscle spindles. By maintaining a state of balanced tension, posture and uprightness can be sustained for lengthy periods and reflexes maintained in a condition of semi-readiness. However, muscle tone will be increased if the gamma efferent system is abnormally facilitated by overactivity of the descending BSRF motor system. Such a sequence will produce hypertonic rigidity and contractions in extensor and other skeletal muscles. Such a model probably provides the simplest conception of the electrogenesis of convulsive movements, irrespective of how the GSA has been initiated at the cortical level. Nevertheless, a definitive account of the neuromuscular systems and processes involved in the motor components of seizure activity is still awaited (Aird et al., 1984; Engel, 1989).

Once the brief excitatory phase of the seizure has been terminated, the activity of the descending BSRF will convert to a state of neuronal quiescence. This is due either to functional exhaustion of the system or to an engaged inhibitory procedure involving the bulbar reticular formation which is in turn controlled by cortical and subcortical mechanisms. In any case, the normal modulatory and energizing effects of the motor branch of the BSRF on spinal motor centers will be temporarily suspended, lost or at least wane in influence. An inhibitory hypotonic-like state will prevail with skeletal muscles becoming flaccid and reflex responses unable to be elicited. This will usher in a period of behavioral depression and loss of movement which, in the case of concussion, represents a more prominent and familiar symptom than that of the initial excitatory phase. This is likely to involve the concussed patient falling down or continuing to lie limply on the ground. If just stunned, the victim may struggle to remain upright.

Finally, it will be recalled that the reticular theory of concussion provides basically the same explanation for the disruption of motor function as is outlined above for the post-ictal or secondary depressive phase. The main difference between the two theories in this respect is that the reticular theory imagines the paralysis of BSRF activity as being due to a more or less direct traumatic insult. Otherwise, it is in this aspect that the convulsive and reticular theories of concussion are most congruent.

5.5.11. 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 and Van 'T Hooft, 1975). These have been summarized elsewhere in the present article (Sections 1 and 5.5.3) 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 spon-

taneous 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 and 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 and Marmarou, 1991).

5.5.12. 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 and Reynolds, 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 and 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 and 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.

5.5.13. The effects of generalized seizure activity on somatosensory evoked potentials

If the convulsive theory is correct, then it would be predicted that the effects of concussion on EPs and the EEG should be the same or similar to those of GSA. The earlier analysis which concluded that concussion induces an acute state of excitation within the spontaneous cortical rhythms helped to confirm this prediction (Section 4.1.3). With regard to the EPs, the effects of concussion on the cortical SEP have now been documented in a fairly definitive manner (e.g. Letcher et al., 1973; Ommaya and Gennarelli, 1974;

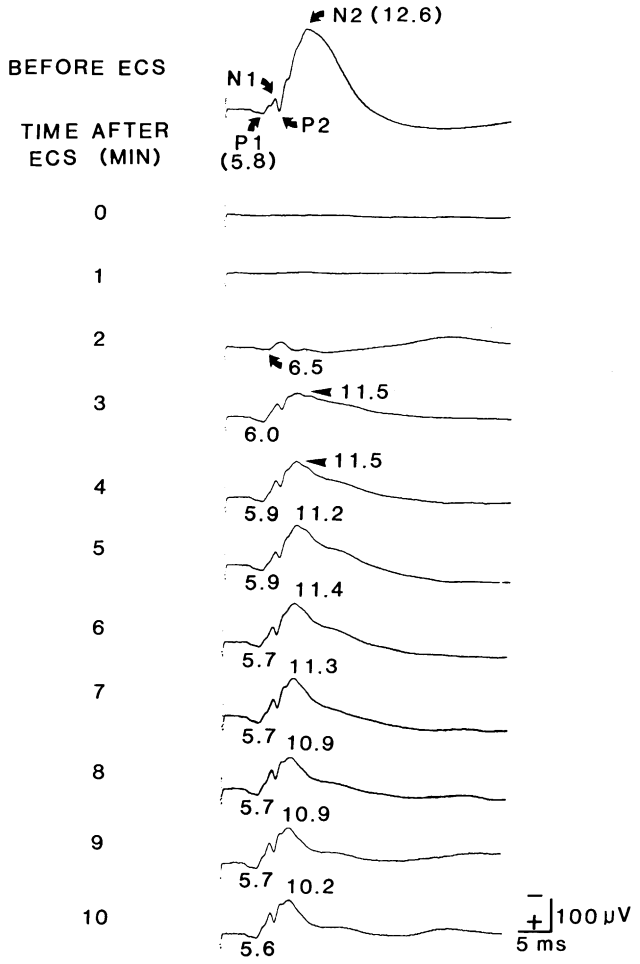

Fig. 4. The first of three examples of the effects of electroconvulsive shock (ECS) on the cortical SEP in the rat. Each set of data is derived from a single animal. The baseline SEP was recorded just before the induction of generalized seizure activity by ECS. Subsequent SEPs were recorded at the times indicated after ECS. In the baseline (before ECS) SEP, the four principal components of the waveform are identified with the actual latency of the P1 and N2 components in parentheses. In the following SEP traces, only the latency values of P1 and N2 are indicated. It should be noted that the traces illustrated in this figure and in Figs. 5 and 6 were all recorded using a time base of 50 ms. This is in contrast to the SEPs illustrated in Figs. 1–3 which were recorded using a shorter analysis time of 20 ms.

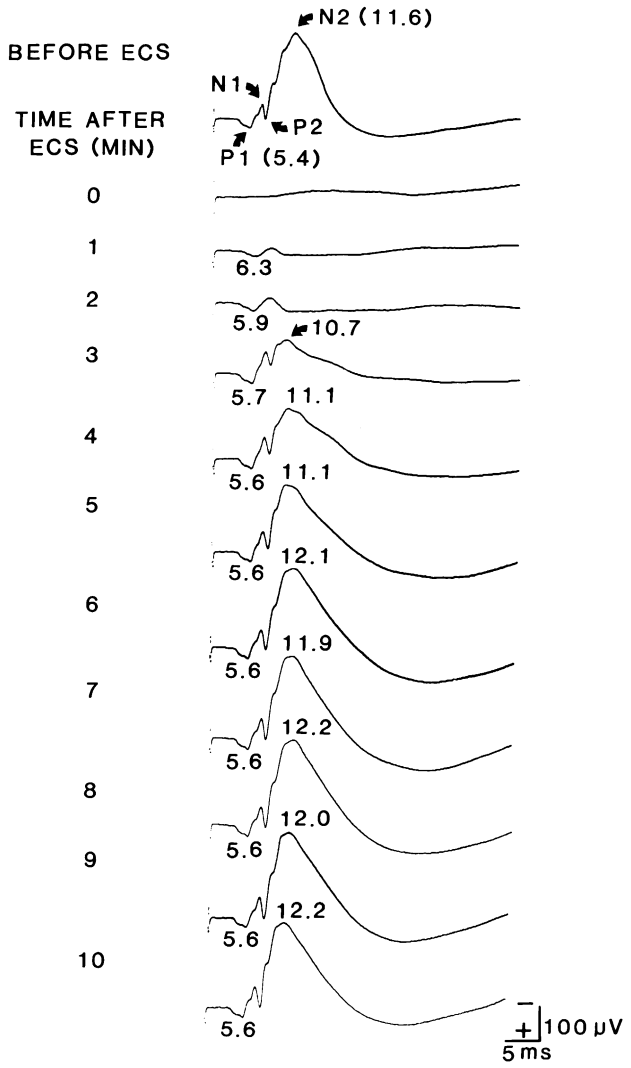

Fig. 5. A second example of the effects of ECS on the rat's cortical SEP.

Shaw, 1986a). It would therefore be expected that the effects of GSA on the cortical SEP should largely mirror those inflicted by a concussive blow.

These predictions have been tested when GSA was induced electrically using ECS (Shaw, 1985b). The effects of ECS were examined on the cortical SEP in the rat and the findings may be compared to similar SEP recordings made following experimental concussion (Figs. 1–3). Three examples of the effects of ECS on the SEP are illustrated in Figs. 4–6. Immediately after the induction of GSA, the cortical waveform was invariably lost but rapidly reappeared during the post-ictal period. The short-latency potentials were restored first, albeit with a small increase in latency. Return of the basic waveform seemed to roughly accompany the animal regaining its responsiveness. By the end of the 10 min post-ECS recording period, the only residual abnormality in the SEP was an often persisting depression in the voltage of the late secondary component (N2). If these three recordings are compared with the three concussion illustrations (Figs. 1–3), it can be appreciated that the pattern of change in the waveform under both conditions is remarkably similar. Such a resemblance is therefore consistent with the notion that GSA is the common mechanism of action underlying the temporary loss of the cortical SEP following either the administration of ECS or a concussive blow.

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

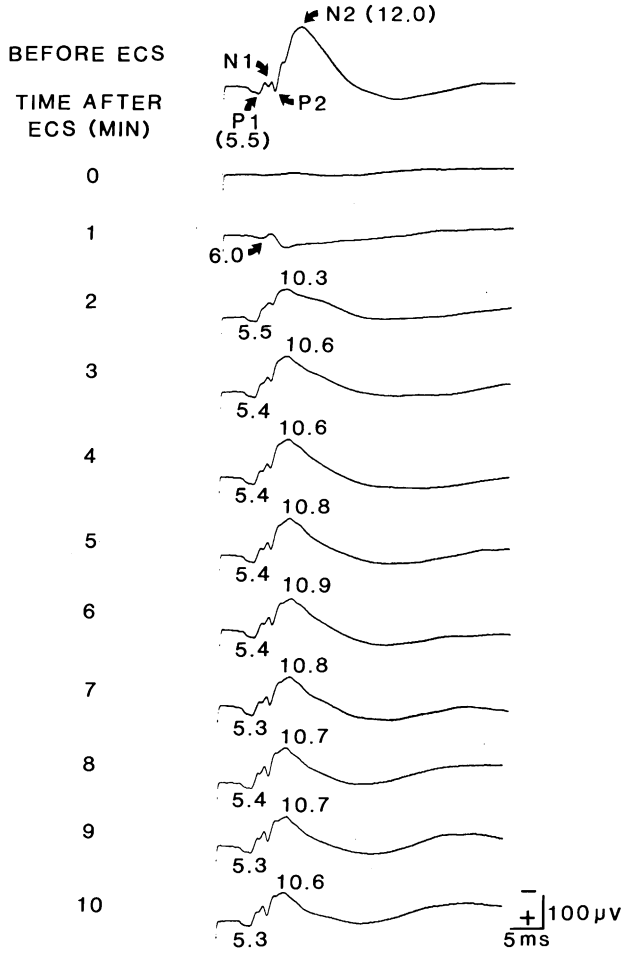

Fig. 6. A third example of the effects of ECS on the rat's cortical SEP.

and experimental petit mal seizures (e.g. Mirsky et al., 1973; Mirsky and Orren, 1977). Notably, the waveform is typically not as severely suppressed as with a grand mal seizure.

6. Why doesn't the woodpecker knock itself out?

While a wide variety of vertebrates seem to be susceptible to a concussive blow, a diverse minority are reputed to be virtually immune. These range from birds such as the nuthatch and woodpecker to mammals such as the billygoat and ram. These animals are believed to be able to routinely withstand accelerative or decelerative forces one hundred times greater than can be tolerated by humans (Ropper, 1994). The question of why some animals are invulnerable to concussive trauma is not merely of curiosity value. A successful theory of the pathogenesis of concussion must be able to cope not only with why many animals succumb to it but equally why others are able to resist this type of cerebral insult. Also, any understanding of the biodynamic mechanisms which prevent the occurrence of concussion might lead to the development of more effective prosthetic devices to protect against head injury.

Of the various animals which seem impervious to concussion, most attention has been paid to the woodpecker. Indeed, this is the aspect of the bird's behavior which seems to most fascinate the layman. It is sometimes rather misleadingly expressed as why don't woodpeckers get a headache? (Winkler et al., 1995). The woodpecker is the name given to a group of scansorial and insectivorous birds of which there are more than 200 species. Among its distinctive features, the woodpecker possesses a strong, straight chisel-like bill with which it can incessantly pound on a tree trunk with astonishing force. According to May et al. (1979), as the beak tip strikes the wood, the impact velocity may be 6–7 m/s with an impact deceleration of about $1000 \times g$ (10,000 m/s^2).

The woodpecker's capacity for high powered repetitive pecking plays a central role in almost all aspects of its lifestyle (Sparks, 1969; May et al., 1976a; Winkler et al., 1995). Among its more important functions is the percussive tapping or probing of wood and bark in order to locate cavities where prey (e.g. insects, grubs or other larvae) may be hidden. The bird gains access to the potential food source by drilling or boring into the tree, often retrieving food with its long, sticky, barbed tongue. In addition, the woodpecker excavates large holes in the trunk or branches for the purpose of roosting or nesting, or chisels out funnel shaped holes for food storage. The woodpecker may also engage hundreds of times per day in a related activity usually described as drumming. This is an instrumental equivalent of singing in other birds and typically involves the bill beating a rapid and repetitive tattoo on a hollow dead branch. Drumming appears to play a role in courtship rituals and territorial signaling. It differs mostly from the standard hammering, pounding, drilling performance in that while the rhythm is faster, much less force is exerted.

As May et al. (1976a) have wryly commented, such high speed hammering of the head might have been expected to leave the forest strewn with stunned or brain damaged woodpeckers. That this is not the case, seems to be of more interest to the neuroscientist than to the ornithologist. For instance, a recent text on the behavioral biology of the woodpecker devotes just a single paragraph to this matter out of more than 400 pages (Winkler et al., 1995). In contrast, a paper published in the *Lancet* by the major researchers in this field (May et al., 1976a) triggered a minor avalanche of correspondence on the topic of woodpeckers and head injury.

Precisely what are the mechanisms which protect a woodpecker from concussive injury are unknown. Winkler et al. (1995) have suggested that the reason the bird can escape unscathed even after multiple impacts can most likely be attributed to a number of interacting factors. While this is probably true, at least some of those that have been proposed are of suspect relevance.

One common idea is that the small size and weight (1–4 g) of the woodpecker's brain are the crucial factors. This might at least partially relate to the low brain weight to surface area

ratio (May et al., 1979). However, this is an unconvincing explanation. As noted in Section 5.5.4 of the convulsive theory, it is not at all unusual to witness birds (presumably with brains not much larger or smaller than the woodpecker's) being accidentally concussed. They fall to the ground and lie still for a period but subsequently fly away indicating they had suffered no structural injury (May et al., 1979). Also, mammals with comparatively small brains seem just as readily concussed as higher primates. Much of the research discussed in the present review is based on data from such animals. There seems little reason to believe that brain size or weight is an important determinant of an animal's vulnerability to an ordinary concussive blow.

A second possibility is that sturdy, elastic connective tissue between bill and skull might curtail or diminish the transmission of shock waves arising from the force exerted by the beak striking the tree (Gordon, 1976; May et al., 1976a). While such a tactic might protect the brain from hazardous impact forces, it would also seem to be a largely self-defeating maneuver (Spring, 1965; May et al., 1976b). This is because any such shock-absorbing mechanisms would markedly degrade the potency with which the beak could strike the wood and therefore nullify its utility.

A third explanation is that the hard compact solid bone which comprises most of the woodpecker skull may help shield it from concussive injury. Gordon (1976), one of the advocates of this idea, has observed that other birds that hammer or dive such as the nuthatch or gannet invariably have poorly pneumatized skulls. Nonetheless, whether there is really any direct relationship between degree of pneumatization and susceptibility to concussion is uncertain. A bird such as the kiwi also has a similarly dense skull but it uses its beak for more gentle probing of the soft forest floor rather than high speed drilling into wood. It is likely therefore that the most significant role of a heavy solid cranium is to increase the efficacy of the head as a hammer.

Probably the most long-standing explanation for why the woodpecker is immune to concussion is another variation of the shock absorber theory. May et al. (1976a) cite a number of adherents to this notion during the past half century (e.g. Bock, 1964; Spring, 1965). According to this, the powerful muscles of the head and long neck which propel the neck back and forth have a dual function. They not only control the rapid head movements but, in a contracted state, they also reciprocally absorb the energy generated by the bill-wood collision. By this action, potentially injurious impact forces are diverted away from the brain and are subsequently dispersed and dissipated elsewhere in the body via neck muscles and ligaments. Such a theory is dependent upon the beak being partially insulated from the skull so providing an opportunity for the shock waves to be re-routed away from the cranium (May et al., 1976a). The most prominent muscle involved in this process is thought to be the protractor pterygoidei. The woodpecker's exceptionally extensible tongue is controlled by the geniohyoid muscle. This muscle drapes around the skull from the rear and has also been conceived as having a shock absorbing capacity, although this remains a controversial proposition (May et al., 1976a; Gordon, 1976; Winkler et al., 1995).

May et al. (1979) reasoned that no structural aspect of the skull or head could provide a completely satisfactory account of how the woodpecker can evade concussion. Instead, these investigators decided to determine the trajectory with which the head and beak were propelled toward the wooden surface. Initially, they examined nature films provided by Walt Disney Productions. However, these proved disappointing as the films were shot at too slow a rate (24 frames/s) to provide useful information about the action of the bird's head. As an alternative, high-speed cinematography was employed to capture head movements of a disabled woodpecker which lived in a park ranger's office. This bird could not fly because of a wing injury but otherwise its pecking behavior appeared intact and enthusiastic. The woodpecker was photographed using both color (400 frames/s) and black and white (2000 frames/s) film. Head movements were analyzed frame by frame by plotting various landmarks such as the position of the vertex, eye and beak. This was done both by visual inspection (using color film) and by computer analysis following digitization with a microdensitometer (with the black and white footage).

Irrespective of what technique was employed, the findings were always the same. They revealed that the bird's head and bill attacked the wooden target in a fundamentally straight-line manner. This indicated that the decelerative impact with which the tip of the beak struck the tree was linear rather than angular in origin. May et al. interpreted this discovery as being consistent with Holbourn's theory that it was sudden rotational movements of the head possibly generating peripheral shearing type of injury in the brain which was principally responsible for concussion. In addition, the trajectory studies of the woodpecker head were also compatible with the experiments of Ommaya and Gennarelli (1974) using the squirrel monkey. It will be recalled that concussion always ensued following angular acceleration of the head of the squirrel monkey but never after translational (or linear) acceleration (Section 4.2.2).

Ostensibly, therefore, the strike-path analysis appears to have solved a major part of the puzzle as to why the woodpecker and possibly some other animals are largely immune to concussive insult. May et al. (1979) also observed that the trajectory data seems to provide compelling circumstantial evidence regarding the role of a particular type of head movement in the prevention of concussion. Propulsion of the Woodpecker's head along a horizontal plane would be neither the most simple nor most efficient movement for tapping, hammering or drilling wood when compared with more angular motions. Therefore, if the bird is prepared to sacrifice optimum pecking performance as well as to maintain a more intricate neuromuscular system in order to control it, this probably indicates that linear movement must possess some compensating protective benefit.

A subsequent Editorial in the *Lancet* (Editorial, 1979) described May et al.'s findings as remarkable. Yet, beguiling though their argument might seem as an explanation for the woodpecker's resistance to concussive injury, it is still less than entirely convincing. The principal difficulty lies in the fact that while translational acceleration never produced concussion in the squirrel monkey, it nevertheless could still inflict significant cerebral damage after just a single blow (Ommaya and Gennarelli, 1974). It would be expected, therefore, that the cumulative effects of sustained hammering would be a rapidly wrecked brain even if the woodpecker had managed to survive being actually knocked unconscious.

It is also uncertain whether the hammering and pounding motion of the woodpecker's head is exclusively linear in nature. Normally, translational and rotational components of inertial loading of the head would be expected to co-exist (Section 3). The *Lancet* Editorial cites the earlier research of Spring (1965) who demonstrated that as the intensity of the hammer blows increased, so the angular movement of the head became more pronounced. It is, nonetheless, conceded that such recordings were made using less advanced photographic equipment than was available to May and co-workers. Still, a consideration of the findings of Ommaya and Gennarelli (1974) and Spring (1965), as they relate to the linear trajectory data of May et al., would tend to suggest that there may be yet more factors operating to shield the woodpecker from concussive trauma.

In their early anatomical studies, May and co-workers had prepared frozen sections of the woodpecker head (May et al., 1976a). Control sections were made from the toucan, a bird which is related to the woodpecker family but otherwise does not hammer. The authors reported that the woodpecker's brain was securely and firmly encased within the skull by what they described as dense spongy bone. The subarachnoid space was very constricted and consequently there would be only a minuscule amount of CSF present. Judging by these findings, it can be concluded that the woodpecker's brain is carefully stowed within the cranium with virtually no freedom to move at all.

The convulsive theory as outlined in the present article would predict that an animal such as the woodpecker would most likely escape concussion by preventing paroxysmal rotation (and therefore mechanical depolarization) of the brain within the skull. As Denny-Brown and Russell (1941) demonstrated, one simple and relatively effective means of achieving this would be to keep the head as still as possible. This is obviously not an option for the woodpecker. Nonetheless, practically the same result could be attained by tightly restraining the brain within the skull, even if the head was concurrently exposed to sudden impact or movement. Although May et al. (1976a) chose not to interpret their anatomical studies in this manner, their findings are almost perfectly in accord with the expectations of a convulsive model of concussion.

Not surprisingly, the woodpecker appears to have evolved a structural arrangement for avoiding being concussed which is basically just a variation of the strategy adopted by the football player, the pugilist or assault victim to minimize the chances of being knocked out. In the case of clinical concussion, prevention involves control of head movement. By contrast, prevention of concussion in the woodpecker would seem to involve control of brain movement. Irrespective of which technique is employed to stop the roiling motion of the brain which is assumed to initiate a concussive episode, the net result and the mechanical principles operating are basically the same. In both instances, the kinetic energy which is either absorbed or released by the head at the time of the accelerative or decelerative impact is allowed to flow harmlessly through the brain before being diffused elsewhere in the body. In the case of the woodpecker, this process of transmission and distribution might well be abetted by its solid dense skull and well endowed head–neck musculature. Perhaps the biggest handicap to an understanding of why an animal such as the woodpecker can escape being concussed has lain in the lack of a coherent theory of concussion. One of the advantages of the convulsive theory is that it can explain the significance of why the woodpecker possesses a tightly packaged immobilized brain.

6.1. Head clash in the ram

The explanation offered above as to the invulnerability of the woodpecker to concussive injury remains a tentative one. One method of helping to confirm it would be to examine the relationship between skull and brain in other animals which also seem to be exempt from concussion. Apart from the woodpecker, probably the most notable example of this immunity is the ram. These animals indulge in a ritualistic type of intraspecies fighting which is usually labeled head clash (Hart, 1985; Houpt, 1991; Lynch et al., 1992). This behavior typically involves a pair of rams simultaneously rushing at each other. The resulting head to head (or head to horn) impact is powerful and ferocious. Yet, like the woodpecker, the ram suffers no concussion from the head blow. The purpose of such activity seems to be to establish dominance and social status among the flock without the animals sustaining significant injury (Lynch et al., 1992). As such, the process of charging and head butting may continue until one capitulates and shifts elsewhere.

Unlike the woodpecker, there seems to have been little consideration given to why head clash in the ram does not result in the animal being knocked out or stunned. Hart (1985) has remarked on the role of the ram's thick skull and large sinuses in protecting it from head trauma. Be that as it may, it might be predicted that a similar anatomical organization would exist for the ram as for the woodpecker. This would include a tightly fitted brain with a markedly narrow subarachnoid space when compared with appropriate controls. It might further be predicted that this sort of relationship between skull and brain could also be present in sheep in general because ewes may engage in combative

head bunting and ramming behavior as well (Hart, 1985; Lynch et al., 1992).

Unfortunately, any consideration of how rams escape concussive injury during head clash immediately exposes a latent contradiction. It seems unlikely that an animal such as the woodpecker can ever be concussed under any natural circumstances. The same cannot be said of the sheep. It will be recalled from the section on EPs that both male and female sheep are routinely and reliably concussed using the captive bolt prior to being slaughtered (Section 4.2.4). On the face of it, it would be hard to reconcile this discrepancy in the animal's vulnerability to concussive trauma if it is assumed that it possesses a brain protective mechanism similar to that of the woodpecker. Instead, it suggests that the ram (and possibly sheep in general) may be relying on the same behavioral repertoire that humans use to avoid being concussed when they can anticipate an imminent blow. This principally involves tightening the neck and head muscles and flexing or lowering the head (Strich, 1961; May et al., 1979). If the ram relied on this technique, it would not necessarily have to have its brain embedded in the skull like that of the woodpecker. This would explain the apparent paradox of why the animal was also vulnerable to an unanticipated concussive blow such as delivered by the captive bolt. Nonetheless, this sort of ploy might seem a rather risky and uncertain means of consistently evading TBI during combative behavior such as repeated head clashing.

There is a further intriguing twist to the problem of why an animal such as the ram can apparently sustain a concussion under some conditions yet engage in head clashing behavior with impunity. This concerns the respective use of the penetrative and non-penetrative types of captive bolt with different species of farm animals. Use of the captive bolt is often described as percussive stunning but its two versions would seem to have quite different mechanisms of action. Describing the use of the non-penetrative captive bolt as an example of percussive or compressive concussion is really a misnomer. Shooting with the non-penetrative bolt accelerates the freely moving head setting any relatively unrestrained brain rotating, shifting or swirling within the cranium. Such a technique is not much different from that used by West et al. (1982) to produce acceleration concussion in the rat using a lead-tipped dart fired from a spring-loaded pistol. In contrast, use of the penetrative captive bolt would seem to represent a more genuine example of percussive stunning. It is not much different from direct cortical impact models of compressive concussion where a pneumatic impactor strikes the exposed cortex (Dixon et al., 1991). In both instances (penetrative and non-penetrative) it is envisaged that concussion ensues because the indentation and deformation of the cortical tissue sets off a process of mechanically-induced depolarization.

According to standard procedures for humane slaughter, cattle are, as a rule, initially concussed using the non-penetrative bolt. This would imply that the cattle brain, like that of the primate, must be relatively free to move within the cranium. It is notable that while cattle do engage in aggressive head to head struggles, this is normally just a maneuver to gain access to an opponent's flank where the principal injury is inflicted (Hart, 1985; Houpt, 1991). In contrast, those ruminants which participate in charging and head clashing attacks (such as sheep and goats) are stunned using the penetrative bolt. Such a practice would be consistent with the notion that at least some ruminants do possess a brain fixed firmly by the surrounding skull akin to that of the woodpecker. This facility should render them largely immune to standard impact accelerative trauma such as the non-penetrative bolt or head clash. However, even a rigidly constrained immobilized brain would not be protected from a percussive blow when it is delivered directly to the cortex such as with the penetrative bolt. If an avian model of the cortical impact device was developed, it would be predicted that even a woodpecker would be susceptible to concussion under such circumstances. Comparative neuroanatomical studies among selected ruminants should help determine just how accurate such speculations are.

7. 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 the present review 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.

Considering that epileptic fits and concussive trauma must have been more common in historic times than they are today, it defies belief that the impressive similarity between the two conditions was not recognized long ago. Be that as it may, there does not appear to have been any formal acknowledgement of a possible relationship between concussion and a generalized epileptic seizure until the conjectures of Duret, Symonds and Walker during the first half of the 20th century. Why the convulsive theory has not attracted more attention, despite accumulating evidence in its favor, is not entirely clear. Part of the reason, as Walker (1994) hinted, is because of the long shadow that the discovery of the ARAS has cast over the whole subject of the physiology of unconsciousness during the past 50 years. In addition, the reticular model could provide a relatively simple and coherent explanation for loss of consciousness. In contrast, it has never been especially plain exactly how convulsive

activity of any kind actually induces loss of responsiveness and awareness. Walker et al. (1944) do not directly address this issue at all. There could also be a more nebulous reason. Concussion is characterized by behavioral inhibition and paralysis, so it might seem counter-intuitive and even paradoxical that such a state of depression could be initiated at the physiological level by neuronal excitation.

Denny-Brown and Russell (1941) demonstrated that a standard clinical concussion must be contingent upon the transfer of sufficient kinetic energy during a sudden change in the momentum of the head. This could be due to either an abrupt increase (acceleration) in head movement or sudden arrest of head movement (deceleration). According to the present conception of the convulsive theory, angular acceleration of the head should impel the partly tethered gelatinous mass of brain to rotate turbulently within the confines of the cranial vault. The swinging, swaying, rolling, swirling or jarring motions set up should increase the chances that the cortical surface of the brain will dash itself against the boney walls of the interior skull. If any such contact is sufficiently violent, then the cortical tissue will be deformed, indented, compressed or stretched. Even in the absence of more overt damage, such mechanical stimulation should be adequate to open mechanosensitive ion channels. This should allow for an influx of sodium and calcium ions thereby triggering a process of membrane potential breakdown, neuronal excitation and discharge. Once the PDS begins to form, the sequence of events underlying the development of a state of GSA including burst firing, recruitment, spread and subsequent demise, is conceived as being basically the same as that which occurs during a spontaneous epileptic attack.

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. As described in the Section 5.5.1, 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. Further, a convulsant mode of action can reconcile the appearance of epileptiform activity in the acute post-traumatic EEG with the simultaneous abolition of the cortical EP. 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. It is obvious that such a conception of loss of consciousness is rather more akin to the cerveau isolé preparation of Bremer than it is to the ARAS/BSRF model of Moruzzi, Magoun and Lindsley. In its present incarnation, therefore, the convulsive theory finds little or no role for the ascending arousal component of the BSRF in the induction of concussion. 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, 1997). 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 and Sampson, 1974; Gronwall and 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.

This explanation could therefore account at least partially for findings such as those of McMillan and Glucksman (1987). In this instance, a group of concussed patients were compared with a control group who had suffered just orthopedic injuries. The authors confirmed the basic findings of Gronwall and Wrightson using the PASAT but only when the information to be processed was presented at a fast rate. When a slower (presumably less stressful) rate was employed, there was no evidence of cognitive impairment in either group. Nor did the concussed group perform in an inferior manner on standard tests of

memory and intelligence. Such findings are consistent with the idea that the subtle impairments in intellectual function revealed by tests such as the PASAT maybe more likely to reflect elevations in stress and anxiety levels than to be due to some kind of residual organic damage.

The convulsive theory may also help to resolve the long-standing controversy concerning the relationship between concussion and more serious craniocerebral trauma. The quantitative view favored by Symonds (1962) and exemplified in the centripetal theory conceives blunt head injury as a continuum with severe types of trauma differing only by degrees from milder concussive injury. A common understanding is that widespread white matter degeneration (or DAI) caused by tearing and stretching of neuronal tracts underlies the more serious types of closed head injury which may result in a long-term comatose state. In contrast, the pathobiological basis of concussion is conceived as being just a minor, reversible and dysfunctional form of DAI. By comparison, the convulsive theory implies that concussion has a quite distinct pathogenesis which is qualitatively different from more serious types of TBI.

If concussion differs qualitatively from more severe types of head trauma, then it follows that a successful animal model of experimental concussion may not necessarily be valid for more serious kinds of cerebral injury in humans. It is the contention of the present review that an effective experimental model of concussion mechanically induces depolarization of cortical neurons by one means or another and thereafter a short-lasting state of generalized cerebral excitation. Increasing magnitudes of the mechanical force may therefore inflict progressively greater neuronal injury throughout the brain in addition to GSA but without necessarily replicating the functional and structural damage that occurs in human head injury. Such a discrepancy may be at least part of the reason for the so far disappointing results from clinical trials attempting to assess the efficacy of a variety of neuroprotective agents in severely head injured patients. Reputed to be among the most promising agents under these conditions are corticosteroids, calcium channel blockers, free-radical scavengers and NMDA receptor antagonists (Kahn and Bondr, 1997; Maas et al., 1999). In their recent review, Maas and co-workers cite patient selection, methodological flaws and other clinical factors as among the reasons which could account for the failure of these trials to demonstrate improvement of outcome. However, the authors consider only tangentially any contribution of inappropriate experimental animal models. What is not stated specifically in this review is that the origins of at least some of these clinical trials lie in animal experiments developed using the fluid percussion model of head injury or some similar device. It was previously argued (Section 5.5.7) that this technique is a potent experimental model of concussion basically because the application of the fluid pulse efficiently and directly deforms, indents, compresses or otherwise stimulates cortical tissue. More intense fluid percussion injury may cause widespread histopathological changes especially within the brainstem. While these may be susceptible to certain kinds of pharmacological intervention, they could also be largely unrelated to the pathophysiological processes underlying severe neurotrauma in humans. This characteristically does not involve discrete primary brainstem injury (Section 5.3.2). Any success of such agents under these artificial conditions might therefore be extrapolated to a clinical setting with caution.

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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