4 PRIMARY AND SECONDARY BRAIN INJURY

A. David Mendelow and Peter J. Crawford

4.1 Introduction

Throughout most of the world, the majority of head-injured patients are initially managed by emergency medical services that do not have specialized knowledge of the pathophysiology and treatment of head injury. It is for this reason that the traditional division into primary and secondary brain damage remains useful; primary brain damage occurs at the time of impact, produces its clinical effect almost immediately and is refractory to most treatment. By contrast, secondary brain damage occurs at some time after the primary impact and is largely preventable and treatable. The clinician’s role, therefore, is to recognize and document the primary brain damage, then to prevent and treat secondary brain damage. Recent research has shown that, although primary brain damage has been regarded as irreversible, changes in ultrastructure, the blood–brain barrier and neuronal function may progress over time and may provide some potential for treatment (Povlishock 1992, 1995; Maxwell, 1995).

Understanding this concept prepares the non-specialist clinician for the main challenge in head injury management: the prevention and treatment of secondary brain damage. It is therefore essential that all the causes and consequences of secondary brain damage are known and understood. In an ideal world, no secondary brain damage would occur! Also, this concept paves the way for understanding how neuroprotective strategies (hemodynamic and pharmacological) may limit secondary brain damage. There is also merit in classifying brain damage into focal and diffuse types (Teasdale, 1995) but, from the clinical standpoint, the division into primary and secondary damage remains the most pragmatic and therapeutically useful classification.

Secondary brain damage may begin very rapidly after impact, so that decisions must be taken early and correctly. Globally, many more lives would be saved and the morbidity from head injury would be more effectively reduced if head injury management and services were better organized than could ever be achieved by improving the intensive care and pharmacological treatments in already well-developed areas and centers. Unfortunately it is this ‘high tech’ emphasis that has dominated thinking and practice in head injury management to date.

This concept and such organizational challenges have been recognized for many years, and a group of British neurosurgeons (Group of Neurosurgeons, 1984) produced guidelines for head injury management that have become a consensus document adopted throughout the UK and now in many other parts of the world (Garibi, 1995, personal communication). More recently, such guidelines have been modified to include recommendations for children, and the Society of British Neurosurgeons has endorsed new guidelines. Their introduction has resulted in an increase in the number of hematomas being detected in large regional centers (Miller, 1993; Treadwell and Mendelow 1994; Figures 4.1, 4.2). A similar set of guidelines has recently been produced in the United States, under the auspices of the American Association of Neurological Surgeons.

The prime aim of such guidelines is:

- to reduce initial hypoxic ischemic damage using principles of resuscitation set out in the Advanced Trauma Life Support system (ATLS – American College of Surgeons, 1993);
- to increase the early detection of hematomas so that delay in treatment can be eliminated.

Although the ATLS recommendations play a vitally important role in preventing hypoxia and ischemia, the ATLS approach to head injury is not practical throughout most of the world. The ATLS statement ‘All head injuries except the most minor will require a CT scan’ would result in the successful diagnosis of
most hematomas, but could not be implemented universally because of the lack of local 24-hour emergency CT facilities in most countries (Hewer and Wood, 1989). It is for this reason that guidelines for head injury are more applicable to cities, towns and regions without local 24-hour CT scanning facilities for all head injuries. Since they are based on risk factors for traumatic hematomas (Mendelow, Teasdale and Jennett, 1983; Teasdale et al., 1990), they should result in correct diagnosis of the majority of traumatic hematomas by selecting for transfer those head-injured patients who are most at risk of developing hematomas. They would be transferred to centralized neurotrauma units where 24-hour scanning is available. Similarly, the advanced pediatric life support (APLS) program (APLS, 1993) has made recommendations for CT scanning that may not be practical in many small centers because of the limited availability of after-hours scanning.

### 4.2 Primary brain damage

The pathology of brain damage has been discussed in Chapter 3 and will not be discussed in great detail here, other than referring to its importance in determining the initial level of consciousness and any focal neurological deficit. Also, the time-related ultrastructural changes that take place within minutes of injury are discussed because of their importance in relation to possible treatment. The clinical effects of this primary (or impact) damage may be greatly aggravated by secondary brain damage (Bullock, Zauner et al., 1995; Ito, Barzo et al., 1995). Thus diffuse axonal injury (DAI), contusions and lacerations of the brain will produce immediate clinical effects varying from concussion, with mild DAI (Oppenheimer, 1968), to coma and death. Focal primary damage, for example with cerebral laceration due to a penetrating injury, may also produce an immediate neurological deficit depending upon the site of injury. Thereafter, any increase in neurological deficit or deepening of the level of consciousness will be due to secondary brain damage.

Recent experimental research has shown that focal axonal swelling occurs within 15 minutes of traumatic brain injury (TBI) due to misalignment of microtubules (Maxwell, 1995) and that their disruption leads to ‘nodal blebs’ within 2 hours. Later there is a change in the axolemma permeability which, after 6 hours, leads to retrograde and anterograde misalignment of neurofilaments (with compaction and mitochondrial

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**Figure 4.1** Effect of 1982 Edinburgh guidelines for management of head injuries on the pattern of traumatic hematomas detected and operated on before (a) (1981) and after (b) (1986/1989) their introduction; odds ratio with 95% confidence limits. a = detected; b = operated. (Source: reproduced from Miller et al., 1992, with permission.)

**Figure 4.2** Effect of two editions of head injury guidelines on head injury admissions to Newcastle General Hospital in the Northern Region of England and number of traumatic hematomas detected. (Source: data from Treadwell and Mendelow, 1994, updated for 1995 data.)
abnormalities). Similarly, blood–brain barrier (BBB) breakdown begins within 3 minutes of injury, leading to albumin extravasation (Fukuda et al., 1995). These early changes following DAI have been confirmed clinically with diffusion-weighted magnetic resonance imaging (MRI; Vink, 1995; Mikulis, 1995; Lenkinski, Gennarelli et al., 1995). Nevertheless, it is superadded secondary ischemic damage that results in cytotoxic edema and elevated intracranial pressure (ICP; Ito, Barzo et al., 1995). The combination of these early changes with DAI and hypoxia/ischemia as a secondary event may provide some potential for pharmaceutical neuroprotection since increases in glutamate concentrations are maximal after secondary ischemia but do not occur when DAI occurs in isolation (Bullock, Zauner et al., 1995).

Tsuji et al. (1995) have shown experimentally that with DAI in rats there is no change in excitatory amino acid (EAA) or extracellular calcium levels unless secondary insults take place as well ($P_{aO_2} < 5.33$ kPa; BP < 40 mmHg).

### 4.3 Secondary brain damage

The classification of secondary brain damage has traditionally been into extra- and intracranial (Table 4.1). There is merit in maintaining this classification.

#### 4.3.1 EXTRACRANIAL SECONDARY BRAIN DAMAGE

Extracranial problems produce secondary brain damage either by hypoxia or by oligemia/ischemia (Table 4.1). The ultimate consequence of either is a reduction in the availability of high-energy phosphate (adenosine triphosphate, ATP). This leads to failure of membrane pumps so that cells either die or become swollen (so called cytotoxic edema). The distribution differs in that hypotension with primary oligemia and ischemia tends to affect the arterial boundary zones (Figure 4.3). By contrast, hypoxemia alone tends to be more global, with neuronal loss, which leads to cortical atrophy in survivors.

The most extreme consequences of severe and prolonged hypoxia are the persistent vegetative state (PVS) or death. PVS may occur with preservation of brain-stem reflexes, but with loss of most of the cortex, although hallmarks of DAI are found in 77% of patients who die in PVS (Graham, Jennett et al., 1995). Secondary brain damage due to hypoxia and hypotension also occurs in patients who have already been admitted to intensive care units, when it is looked for carefully: detailed monitoring studies by Jones and Miller (Jones et al., 1993, 1994; Andrews et al., 1990) with accurate computerized recording have revealed that such insults occur in 32% of head-injured patients even when there is no evidence that these have been detected on standard nursing charts.

If the extracranial insults are associated with intracranial lesions, then the penumbra of any region of hemorrhage or compression becomes the primary target of hypoxemia or ischemia. It has been clearly shown that intracerebral hemorrhage produces an area of ischemia around the hematoma and that this is surrounded by a penumbra of functionally impaired

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<td>Hyponatremia</td>
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<th>Intracranial causes</th>
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<td>Hemorrhage</td>
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<td>– Subarachnoidal</td>
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<td>Swelling</td>
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<td>– Meningitis</td>
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<td>– Brain abscess</td>
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Figure 4.3 CT scan showing bilateral boundary zone infarcts from hypoxia–ischemia.
but potentially viable tissue (Figure 4.4; Mendelow et al., 1984).

Similarly, there is an area of ischemia that underlies an experimental subdural hematoma which is also bounded by a penumbra (Bullock et al., 1990). In all these situations, hypoxic or ischemic extracranial insults will aggravate the secondary damage in relation to the focal lesion. Similarly, extracranial secondary insults will aggravate primary DAI (Bullock et al., 1995; Ito, Barzo et al., 1995).

Regrettably, such hypoxic and hypotensive insults have persisted in patients transferred to neurosurgery units, despite many efforts to prevent them (Gentleman and Jennett, 1981; Gentleman, 1992; Kohi et al., 1984). The consequence is that ischemic brain damage remains a very frequent finding at autopsy in patients who die with head injury. It has fallen only very slightly from 91% in 1978 to just over 80% in 1989 (Graham, Adams and Doyle, 1978; Graham et al., 1989). Hopefully, better emergency rescue and pre-hospital resuscitation will reduce the incidence of ischemic brain damage. The ATLS and APLS courses will probably achieve this with better initial resuscitation.

The effect of hypoxia/ischemia is particularly severe in head-injured patients where ICP may be elevated. It has therefore become recognized that higher levels of CPP are associated with better outcomes from head injury (McGraw, 1989; Mendelow et al., 1994; Miller, 1993; Cortbus et al., 1995; Wong et al., 1995a,b; Contant et al., 1993). Furthermore, autoregulation that has become so well recognized in normal physiological studies becomes disordered following head injury (Figure 4.5).

These ischemic events may be missed when CBF is measured because it is often measured only in the intensive care unit after stabilization has taken place (Mendelow et al., 1985; Obrist et al., 1979; Enevoldson et al., 1976; Matthews et al., 1995; Sharples et al., 1994, 1995). However, studies early after head injury have now confirmed reduced CBF with loss of autoregulation if measured within 8 hours of the injury (Schroder et al., 1993; Chapter 11). The result is that an adult patient with a head injury may require a CPP of 80 or 90 mmHg to maintain normal cerebral perfusion. With increased ICP (e.g. 30 mmHg) this may require a mean blood pressure (BP) of 120 mmHg – it is interesting to realize that the unanesthetized previously normal patient with head injury may achieve this spontaneous rise in BP with the Cushing response, which has been recognized for almost a century now (Cushing, 1901, 1903). However, deeply anesthetized patients may be unable to mount a Cushing response, so clinicians dealing with anesthetized head-injured patients in intensive care units, resuscitation rooms and operating theaters must be aware of the need to maintain adequate levels of CPP. In some instances it may be possible to determine the ‘breakpoint’ or ‘inflection point’ for the lower limit of autoregulation by measuring middle cerebral velocity with transcranial Doppler (Wong et al., 1995a,b). In this way the

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**Figure 4.4** (a) Cross-section of rat brain showing intracerebral hematoma. (b) Autoradiograph of same rat to show larger area of ischemia.

**Figure 4.5** Diagram showing loss of autoregulation following head injury. Cerebral blood flow (CBF) remains constant over a range of cerebral perfusion pressure (CPP) from 50–150 mmHg. Continuous line represents loss of autoregulation.
CPP could be tailored to the individual patient. Early monitoring of these parameters may lead to better acute care of head-injured patients in future, although at present these sophisticated monitoring techniques are not universally available. Nevertheless, less invasive techniques like jugular venous oxygen (JVO₂) monitoring (Piper et al., 1995; Gopinath et al., 1994) and transcranial near infrared spectroscopy (NIRS) may become more practical in future (Germon, 1995). In a recent study, NIRS provided a sensitive means of detecting changes in cerebral oxygenation in 97% of insults detected with CPP, transcranial Doppler or laser-Doppler (Kirkpatrick et al., 1995). By contrast, JVO₂ detected only 53% of these insults.

Other causes of extracranial primary brain damage include hypocapnia (used to treat raised ICP) and severe hypoxemia. Although hyperventilation with hypocapnia can reduce cerebral blood flow, there is doubt about whether moderate hyperventilation can produce ischemic brain damage unless cardiac output is reduced by excessive hyperventilation. It is probably best to maintain the $P_aCO_2$ at around 32 ± 2 mmHg in most patients (Chapter 18).

Hyponatremia after head injury is often due to excess ADH secretion, which results from hypovolemia caused either by fluid restriction or by hemorrhage from other injuries. The excess ADH secretion is therefore appropriate to the hypovolemia but inappropriate to the hyponatremia. Further fluid restriction may aggravate the problem by further increasing ADH levels (Poon et al., 1989; Jackowski, 1992). A clear understanding of the water and electrolyte problems following head injury may need to be determined in each case (Nelson et al., 1981). In general, uncorrected hyponatremia may lead to reduced levels of consciousness and even epileptic seizures. Hyponatremia may also result from the ill-advised and sometimes excessive use of dextrose solutions without any sodium supplementation.

4.3.2 INTRACRANIAL SECONDARY BRAIN DAMAGE

The rate of development of secondary brain damage depends upon the cause. It is universally recognized that hematomas should be evacuated expeditiously. The adverse effect of long delay times with extradural hemorrhage and subdural hemorrhage has been documented in studies from Edinburgh, UK (Figure 4.6; Mendelow et al., 1979) and Richmond, VA (Figure 4.7; Seelig et al., 1981).

With extradural hemorrhage, the time from first recorded deterioration in level of consciousness to operation was less than 2 hours on average in patients who made a good recovery or who were only moderately disabled. Similarly, with acute subdural hemorrhage the time from injury to operation strongly influenced outcome, delays of more than 4 hours from injury being the most significant.

In either case the mechanism of secondary brain damage is direct compression of the underlying cortex causing local ischemic brain damage and brain shift, which causes local zones of ischemia in the brain stem and basal structures, and in the cingulate gyrus (Chapter 18). The ischemic brain damage tends to be focal, but if elevated ICP is unrelieved, leading to reduced CPP, then global ischemic brain damage may occur. Similarly, experimental studies have shown ischemic brain damage surrounding intracerebral hemorrhage (Jenkins et al., 1990; Kingman et al., 1988; Mendelow et al., 1984; Nath et al., 1986, 1987; Nehls et al., 1988; Sinar et al., 1987) and clinical studies with SPECT have confirmed this (Figure 4.8; Wyper et al., 1995).

Ultimately the mechanism of neuronal death is almost always a reduction in ATP with membrane pump failure. This leads to activation of calcium channels, with influx of calcium ions into cells resulting in cell death. The process also leads to a release of excitatory amino acids (EAA), including glutamate and aspartate. These activate the receptor-operated calcium channels, with further calcium influx (Figure 4.9).

Prevention of this calcium influx into cells has offered scope for neuroprotective agents, such as nimodipine,
which block the voltage-operated calcium channels (Mohamed et al., 1985) or the receptor-operated channels (Hatfield et al., 1992; Chapter 7).

The potential for neuroprotective strategies in severe head injury is likely to be maximal when secondary brain damage is due to hemorrhage (intracerebral, subdural and subarachnoid) and ischemia (Chapters 7 and 21).

(a) Traumatic subarachnoid hemorrhage and secondary damage

Experimentally, SAH is associated with delayed breakdown of the BBB (Fukuda et al., 1995), possibly because metallic ions in blood (e.g. iron and calcium) are potent catalysts of free radicals (Cortez et al., 1989). Clinical outcome in traumatic SAH is worse than in

Figure 4.7 Effect of delay (from injury to operation) in acute subdural hematoma. (Source: reproduced from Seelig et al., 1981, with permission.)

Figure 4.8 SPECT scan showing area of ischemia surrounding intracranial hemorrhage. (Source: reproduced from Chocksey et al., 1991, with permission.)
patients without SAH on CT scan and is associated with a higher incidence of secondary hypoxic/ischemic insults (Green et al., 1995). In traumatic SAH Kakarieka et al. (1995) have shown that the calcium antagonist nimodipine produced significantly fewer unfavorable outcomes (6-month Glasgow Outcome Scale) than placebo in a prospective randomized controlled trial, confirming earlier suggestions from the ‘HIT II’ trauma trial with nimodipine that patients with traumatic SAH may respond better to nimodipine than those without SAH (Braakman et al., 1994).

It should be remembered that ‘neuroprotective strategies’ can be organizational as well as pharmaceutical: beneficial effects of early operative evacuation cannot be overemphasized because the deeper the level of consciousness at the time of operation in patients with traumatic hematomas, the worse the outcome (Figure 4.10; Bullock and Teasdale, 1990). For this reason early diagnosis and treatment of hematomas will always be the most effective ‘neuroprotective strategy in dealing with head injury.

The severity of underlying primary brain damage with trauma can vary from almost none (in a patient who is fully conscious, but who later deteriorates) to severe, where the patient may be in coma from the outset. There is more likely to be severe primary brain damage with acute subdural and intracerebral hemorrhage than with cases of extradural hemorrhage, where there may be very little primary damage. This accounts for the classical ‘lucid interval’ that has become so well known with extradural hemorrhage (Jamieson and Yelland, 1968). It puts an added burden of responsibility on those clinicians who manage the many patients with minor head injuries with minimal primary brain damage, because compression from extradural hemorrhage may result from middle meningeal bleeding with a skull fracture in an otherwise minor head injury. This is the basis for recognition of the importance of skull fracture in detecting hematomas (Chan et al., 1990; Mendelow, Teasdale and Jennett, 1983; Teasdale et al., 1990; Santos et al., 1995). If free access to CT scanning is available, all head-injured patients will require a CT scan, as assumed in the ATLS and AANS guidelines. The use of a skull X-ray to detect a fracture then becomes unimportant, but in the absence of universal access to CT for head-injured patients, skull fracture remains one of the most significant clinical and radiological features to help detect hematomas (Table 4.2).

### 4.4 Extradural hematoma

Extradural hematomas (EDH) are extracerebral lesions and thus there may be little or no primary brain damage with trauma. The severity of underlying primary brain damage with trauma can vary from almost none (in a patient who is fully conscious, but who later deteriorates) to severe, where the patient may be in coma from the outset. There is more likely to be severe primary brain damage with acute subdural and intracerebral hemorrhage than with cases of extradural hemorrhage, where there may be very little primary damage. This accounts for the classical ‘lucid interval’ that has become so well known with extradural hemorrhage (Jamieson and Yelland, 1968). It puts an added burden of responsibility on those clinicians who manage the many patients with minor head injuries with minimal primary brain damage, because compression from extradural hemorrhage may result from middle meningeal bleeding with a skull fracture in an otherwise minor head injury. This is the basis for recognition of the importance of skull fracture in detecting hematomas (Chan et al., 1990; Mendelow, Teasdale and Jennett, 1983; Teasdale et al., 1990; Santos et al., 1995). If free access to CT scanning is available, all head-injured patients will require a CT scan, as assumed in the ATLS and AANS guidelines. The use of a skull X-ray to detect a fracture then becomes unimportant, but in the absence of universal access to CT for head-injured patients, skull fracture remains one of the most significant clinical and radiological features to help detect hematomas (Table 4.2).

### Table 4.2 Risks of traumatic hematoma with skull fracture and altered consciousness for patients attending Accident and Emergency (Source: from Teasdale et al.)

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<thead>
<tr>
<th></th>
<th>No. per million</th>
<th>Absolute risk of hematoma (1 in:)</th>
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<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No skull fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully conscious</td>
<td>7700</td>
<td>7900</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>550</td>
<td>180</td>
</tr>
<tr>
<td>Coma</td>
<td>66</td>
<td>27</td>
</tr>
<tr>
<td>Skull fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully conscious</td>
<td>130</td>
<td>45</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>43</td>
<td>5</td>
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<tr>
<td>Coma</td>
<td>41</td>
<td>4</td>
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<tr>
<td><strong>Children</strong></td>
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<tr>
<td>No skull fracture</td>
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<td></td>
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<tr>
<td>Fully conscious</td>
<td>7200</td>
<td>13 000</td>
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<tr>
<td>Impaired consciousness</td>
<td>250</td>
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<td>Coma</td>
<td>11</td>
<td>12</td>
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damage, so that, initially, consciousness may recover or be preserved – this accounts for the well known ‘lucid interval’ that occurs with EDH (although it occurs in less than 25% of cases). The frequency of skull fracture with extradural hematoma in children is 79.3% (Santos et al., 1995), which is as high as it is in adults. Furthermore, in infants the large head size relative to the body means that the volume of the extradural space is large in relation to the blood volume, so that hypovolemia may be the primary presenting feature with an infantile extradural hematoma. This, coupled with elevated ICP, leads to a rapid fall in CPP and consequent ischemic brain damage. This is seen particularly in non-accidental injury. For these reasons, monitoring of infants with even minor head injury should include continuous pulse rate recording, and a CT may be indicated if a tachycardia develops.

Posterior fossa extradural hematomas, though rare (less than 5% of all EDH) may give rise to a sudden deterioration in the level of consciousness due to hydrocephalus, and it is important to recognize the need to scan the posterior fossa if an occipital skull fracture is present (Figure 4.11).

A posterior fossa extradural hematoma may extend above the transverse sinus and compress the occipital pole, so that great care must be taken to avoid major blood loss from the confluens sinuum or the transverse sinus when operating on these cases. In children, extradural haematomas are often limited by the adherence of the dura to the sutures (Figure 4.12).

Chronic venous extradural hematomas are rare but may present with late deterioration in level of consciousness (Stevenson et al., 1964). Because these lie at the vertex, CT scanning should include high cuts when a high skull fracture extends over the superior longitudinal sinus.

When a patient with an EDH dies, neuropathological studies usually show massive ischemic damage due to brain compression and/or low CPP.

4.5 Intradural hemorrhage

Subdural hemorrhage and intracerebral hemorrhage were often considered as two separate conditions, and they may well be separate. However, CT and MRI have clearly shown that subdural hematomas often coexist with intracerebral hemorrhage and with cerebral contusions. Acute subdural hemorrhage tends to extend throughout the subdural space and lies mainly on the surface. Although apparently thin, their extensive nature is associated with a larger intracranial volume than would be expected from CT scanning alone. They are usually unilateral and are more frequently associated with underlying primary brain damage, so that patients with acute subdural hematomas are more likely to present in coma, in contrast...
with extradural hemorrhage where primary brain damage is often less severe. The acute subdural hematoma associated with anticoagulants is the exception because in these patients there is often little or no primary brain damage so that they deteriorate, as they bleed into the subdural space, from full consciousness. With time, the subdural hematoma begins to liquefy and by 14–21 days it may have become predominantly liquid so that burr hole drainage may drain it effectively, in contrast with acute subdural hematoma where the solid clot has to be removed via a craniotomy.

Chronic subdural hematomas represent a different spectrum of head injury. The trauma is often minimal or even unrecognized in one-third of cases (Cameron, 1978). Because there may be no primary brain damage in these patients, the outcome is much better than following the treatment of acute subdural hematomas (Nath et al., 1985). In some patients with chronic subdural hemorrhage there is recent acute hemorrhage so that different clot densities can be recognized on CT scans. This recurrent hemorrhage may lead to the development of pseudomembranes which, with time, will result in further liquefaction of the clot. Also, chronic subdural hemorrhage may be bilateral. Such cases may present as dementia rather than as a head injury.

4.6 Intracerebral hemorrhage

Traumatic intracerebral hemorrhage may occur in isolation or be part of a complex intradural hemorrhage. Isolated intracerebral hemorrhage is much more common in the elderly and may at times be difficult to distinguish from spontaneous intracerebral hemorrhage. This is because a primary spontaneous hemorrhage may result in a fall, which causes a secondary head injury. The mechanism of development of traumatic intracerebral hemorrhage is similar to spontaneous intracerebral hemorrhage: an artery or arteriole is disrupted by shearing forces, or ruptures spontaneously, allowing blood under arterial pressure to expand into the brain parenchyma. Bleeding stops when the tissue pressure around the clot reaches arterial pressure. Experimental studies have shown that this type of intracerebral hemorrhage leads to acute ischemia in the immediately adjacent brain. The clot may remain contained within the parenchyma or burst into the ventricle, the subdural space or the subarachnoid space. In contained hemorrhage, there is a ring of ischemia around the hematoma, which in turn is surrounded by a penumbra of functionally impaired but potentially recoverable tissue (Mendelow et al., 1984). The uncontained type of hemorrhage, like subarachnoid hemorrhage, leads to a global fall in CPP with much more widespread ischemic neuronal damage (Nornes, 1975). The pathogenesis of the ischemia has been extensively studied. If an equivalent volume of fluid is injected instead of blood, the volume of ischemia is less than when blood alone is injected (Jenkins et al., 1990) and the area of ischemia is proportional to the volume of blood or fluid injected (Nath et al., 1986). This ischemia and oligemia may be due to mechanical compression of the microcirculation (Kingman et al., 1988). The reduction in CBF and ischemic neuronal damage is also related to the duration of compression, since deflation of a 50 μl microballoon inflated in the rat brain and removed in 10 minutes still leaves extensive neuronal damage and a zone of reduced CBF (Nehls et al., 1988). This suggests that evacuation of intracerebral clots may do little to relieve surrounding ischemic neuronal damage, although removal may reduce ICP by relieving the mass effect. This is clinically logical, since Galbraith and Teasdale (1981) have reported that subsequent deterioration occurs if the ICP exceeds 30 mmHg in patients with traumatic intracerebral hemorrhage. This suggests that surgical treatment is effective for reducing ICP but not for reducing local ischemic damage.

Acute intraventricular hemorrhage and subarachnoid hemorrhage may result in acute hydrocephalus necessitating ventricular drainage although this is rare.

4.7 Herniation

4.7.1 Tentorial Herniation

Apart from elevating ICP and reducing CPP (global effects) and causing local compression and vasoconstriction, hematomas may also cause herniation, the commonest form of which is tentorial herniation. The uncus of the temporal lobe is pushed through the tentorial edge, compressing the third cranial nerve and the posterior cerebral artery. It is common clinical knowledge that a IIIrd nerve palsy following a head injury is a sign of tentorial herniation due to a hematoma, but compression of the posterior cerebral artery is less well recognized. This will produce a medial occipital infarct, which may be the only residual long-term consequence if the clot is removed. These patients may have an homonymous hemianopia on recovery and the infarct may be demonstrable on magnetic resonance imaging (Figure 4.13).

4.7.2 Subfalcine Herniation

Subfalcine herniation may occur as a result of displacement by hematomas. This may cause ischemia due to compression of branches of the anterior cerebral artery (Figure 4.14).
4.7.3 TONSILLAR HERNIATION (MEDULLARY CONE)

Herniation of the cerebellar tonsils is seen particularly with posterior fossa hematomas. The cerebellar tonsils become displaced through the foramen magnum and may be found below the level of C2. This is associated clinically with medullary compression and ultimately brain-stem death.

In conclusion, secondary brain damage from hematomas can have widespread manifestations and consequences but the principle of the diagnosis of secondary brain damage due to a hematoma must be recognized so that this rare complication of head injury (less than 1% of all head injuries who attend Emergency rooms) can be recognized and treated rapidly.

4.8 Brain swelling

Brain swelling may be due to vascular engorgement, or to brain edema. The recognition of venous congestion as a cause of elevated ICP, especially in children (Bruce et al., 1981) led to the widespread use of hyperventilation and hypocapnia in the treatment of raised ICP. More recently, the dangers of excessive hyperventilation have been recognized (Sharples et al., 1994). Venous congestion secondary to cerebrovascular dilatation is also thought to be the mechanism for the generation of A-(plateau) waves of raised ICP (Rosner, 1993).

Brain edema is due to an increase in the water content of brain interstitial space, the neurons or the glia. It has been divided into vasogenic, cytotoxic and interstitial types (Klatzo, 1979). Some have suggested that better terms would be ‘open barrier edema’ for vasogenic edema and ‘closed barrier edema’ for cytotoxic edema (Betz et al., 1989). Recent studies in animal models (Fukuda, Tanno et al., 1995) have shown that blood–brain barrier (BBB) breakdown may occur within a few minutes of injury, challenging the earlier view that vasogenic (open barrier) edema occurred only late after head injury. These workers, however, did show that late BBB breakdown often occurred following SAH, perhaps because the metallic ions in blood are potent catalysts of free radicals (Cortez et al., 1989). Swelling of axons may occur soon after primary DAI because of changes in axolemma permeability (Pettus and Povlishock, 1995) but it is doubtful that this mild axonal swelling would be sufficient to cause whole brain swelling, although it may be associated with transient axonal malfunction. After 6 hours, retrograde and anterograde malalignment of neurofilaments takes place in axons with compaction and mitochondrial swellings. That such mitochondrial abnormalities may occur following traumatic brain injury has been suggested by recent clinical studies in severe head injury in children (Matthews et al., 1996). These mitochondrial changes are rapidly reversible in mild injuries, and may constitute an anatomical basis for concussion (Petrus and Povlishock, 1995).

4.8.1 VASOGENIC EDEMA (OPEN BARRIER EDEMA)

As its name implies, open barrier edema is caused by a change to BBB so that protein leaks into the
interstitial space (Milhorat, 1992). The increased oncotic pressure draws water with it, so that water accumulates between cells. The interstitial space is the primary pathway for clearing extracellular edema proteins. The primary mechanism is diffusion that is independent of pressure gradients (Ohata and Marmarou, 1992). In the direct infusion edema model in the rat, Ohata and Marmarou showed that high- and low-molecular-weight dextrans, as edema markers, moved preferentially towards the cortical surfaces and the subarachnoid CSF.

This type of edema may also develop later around contusions and intracerebral hemorrhage after several days (Marmarou, 1994; Bullock, 1985; Teasdale, 1995; Figure 4.15). In general, vasogenic edema is more common in relation to tumors and abscesses than in head injury. Dexamethasone is effective in reducing vasogenic edema (Todd and Teasdale, 1989). Dexamethasone has not been shown to be effective in head injury although, in one controlled trial of high dose steroids, a subgroup of patients with traumatic intracerebral hemorrhage and contusions seemed to have a better outcome when steroids were given (Grumme et al., 1995).

4.8.2 CYTOTOXIC EDEMA (CLOSED BARRIER EDEMA)

In this type of brain swelling, the cells themselves swell, as the name 'cytotoxic edema' implies. The cause is usually hypoxia/ischemia (either local or global) resulting in a loss of high-energy phosphates and malfunction of the sodium/potassium pumps. Water enters the cells, and calcium channels open, with influx of these ions into neurons. The influx of calcium is itself cytotoxic and results in cell death (Rappaport et al., 1987). Further ischemia may result in the release of free radicals, which change the phospholipid membrane between the ion channels. This aspect is discussed more fully in Chapter 21. Damage to the phospholipid membrane may have a 'knock-on effect', so that the whole cell membrane starts to leak with further influx of calcium and water. Ischemic neurons also liberate excitatory amino acids (EAA) which activate receptor-operated calcium channels in the cell membrane. These include n-methyl-D-aspartate (NMDA) receptors and AMPA (amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors which, when open, also allow the influx of calcium into the cells (Chapters 7 and 21).

Therapeutic initiatives have focused on the use of calcium-channel-blocking drugs and free-radical scavengers as well as NMDA-receptor antagonists (competitive and non-competitive), both experimentally and, more recently, clinically.

The distribution of cytotoxic edema will depend upon the distribution of ischemia, and it may be detected by diffusion weighted MRI (Chapter 14), T2-weighted MRI (if more severe) or CT, in its most severe forms (e.g. stroke), by 8–12 hours after onset. If there is global ischemia due to reduced CPP, infarction and edema will occur in the arterial boundary zones (Figure 4.3). Around or beneath hematomas, cytotoxic edema may remain focal. If large end-arteries are damaged or compressed, there may be an infarct in the appropriate arterial territory (middle, anterior or posterior cerebral artery territory). In each of these situations, there will be a surrounding penumbra of oligemic tissue, which has the potential to benefit from pharmacological and intensive care treatment to optimize CBF and O2 delivery.

4.8.3 INTERSTITIAL EDEMA

Hydrocephalus results in increased intraventricular cerebrospinal fluid pressure, with transependymal exudation of CSF through the ependyma into the brain tissue. This may manifest itself on CT or MRI as periventricular lucency (PVL). Interstitial edema can be relieved by ventricular drainage.

All three types of brain edema may coexist in a head-injured patient, although cytotoxic edema is usually the earliest to appear. The degree of edema in patients with head injury can be measured with gravimetric columns (Shigeno et al., 1982) and this correlates well with the Hounsfield numbers on CT scan (Bullock et al., 1985) and with MRI proton density figures (Marmarou et al., 1990). It is therefore possible to measure the degree of brain edema in patients using CT and MR imaging. These techniques have clearly

Figure 4.15 CT scan demonstrating small left parietal contusion with surrounding edema.
demonstrated the different patterns of distribution of edema in various patients (Figure 4.3). For example, in global ischemia there may be boundary zone ischemia with edema visible on both CT and MRI. Focal edema may occur with infarction as a result of vasospasm from subarachnoid blood (Wilkins and Odom, 1970) or of vessel occlusion (Figure 4.16). Edema may also occur around contusions (Figure 4.15) and intracerebral hemorrhage (Figure 4.17).

**4.8.4 PATHOPHYSIOLOGY OF EDEMA**

Magnetic resonance imaging with diffusion weighting (DWI) has made it possible to characterize different types of edema with apparent diffusion coefficients (ADC), which are reduced in cytotoxic edema and increased in vasogenic edema (Ito et al., 1995). Following DAI in the rat acceleration model, cytotoxic edema has been shown to follow secondary insults. It is likely that these diffusion-weighted techniques will detect changes in tissue water diffusion in the early stages of head injury (Vink, 1995; Chapter 14). Functional imaging, in particular MR spectroscopy, (e.g. N-acetyl aspartate), is likely to reveal lesions that will correlate with clinical and functional deficits.

The plethora of second messenger molecules that produce ischemic neuronal damage and increased water content experimentally is also being shown to be involved clinically, using a variety of techniques, including MR spectroscopy, microdialysis and measurement of CSF and blood/serum levels in patients.

**Figure 4.16** CT scan showing focal ischemia due to traumatic internal carotid artery occlusion (note contralateral subdural hematoma).

**Figure 4.17** CT scan showing acute subdural hematoma, contralateral contusions with surrounding edema and subarachnoid hemorrhage beneath the tentorium and in the perimesencephalic cistern.

The variability of the nature and distribution of edema makes imaging and more accurate time sequence monitoring desirable if effective treatments are to be found in head injury. Using new MRI modalities, it should be possible in the future to differentiate the different causes and time courses of focal and global swelling, each of which may require different treatments – mannitol, steroids, calcium antagonists, NMDA-receptor antagonists, ventricular drainage, free radical scavengers or decompressive surgery.

Perhaps only when we are able to divide the pathology in head-injured patients into relevant categories will we be able to improve outcome. To classify all severely head-injured patients into one disease group (‘head injury’) is unlikely to provide a single effective therapeutic option. This has been well demonstrated in the several large multicenter trials that have failed to identify an individual strategy effective in large heterogeneous groups of head-injured patients (Bailey et al., 1991; Todd and Teasdale, 1989; Ward et al., 1985).

**4.8.5 BRAIN SWELLING IN CHILDREN**

It has long been recognized that brain swelling may occur after even relatively minor head injuries in children (Bruce et al., 1981). Onset may be rapid but sometimes may not occur until days later. Two explanations exist for this rapid onset swelling.
• There is very little space available for expansion within the skull of a child, so that a minor degree of brain swelling produces a marked increase in ICP.
• Children may have a cerebral circulation which responds more actively to trauma than that of adults. Bruce et al. (1981) favor the latter, but studies in Newcastle upon Tyne using receiver-operating-characteristic (ROC) curves were able to demonstrate that ICP and CPP have a much greater effect on outcome in children and young adult patients under the age of 40 than in older patients, where there may be more space available within the cranium (Chambers et al., 1995). This type of secondary brain damage should therefore be anticipated in children and there should therefore be a lower threshold for the institution of ICP monitoring, and (if necessary) ventilation in children than in adults.

It is generally considered that hyperemia is more common in children and, therefore, if there is a role for hyperventilation in the treatment of any patients with head injury, it is likely to be more effective in children and adolescents. Recent studies in children with head injury in intensive care units have shown that cerebral blood flow may fall with long-term hyperventilation used to treat hyperemia (Sharples et al., 1994) so that it may be as harmful as in adults.

The reason for the dangerous delayed brain swelling that sometimes occurs in children with head injury remains uncertain. In 36 children with severe head injury, CBF, CMRO₂ and CMR lactate was measured and it was demonstrated that CMRO₂ fell significantly between 12 and 48 hours while lactate production increased, suggesting a shift to anaerobic metabolism of glucose (Matthews et al., 1996a). Improvement in outcome from severe head injury in children may therefore occur only when continuous monitoring of many biochemical and functional parameters is undertaken and when such results are immediately available to the medical and nursing staff. In addition, monitoring to detect such secondary insults should be undertaken with equipment programmed to provide an alarm when abnormalities take place, because of the unreliability of routine nursing data (Jones et al., 1994).

4.9.1 INFECTION AFTER SKULL FRACTURE

(a) Fracture of the vault

It is very unusual for linear fractures without skin disruption to lead to secondary infection. By contrast, compound linear fractures may allow entry of contaminating bacteria. Compound depressed fractures are far more likely to lead to secondary infection, although the risk depends to a great extent upon the degree of depression, the extent of any contamination and whether or not there has been any penetration. There is also a difference between higher-velocity missile injuries, which impart kinetic energy to the tissues, causing necrosis and extensive destruction of tissue, and the low-velocity (non-missile) type of injury.
more common in civilian experience. The latter is less likely to cause such severe tissue destruction, so recovery of vital tissue is more likely to occur. This may explain why it was always the custom to debride and elevate compound depressed fractures in wartime, and why this teaching influenced the management of non-missile head injuries for many years in civilian practice. Non-missile compound depressed fractures that are not contaminated may be associated with less extensive tissue destruction and may not therefore require extensive debridement and elevation of the fracture (van der Heever and van de Merwe, 1986).

The simple linear and depressed fractures of the vault seen with closed head injury are rarely associated with infection.

(b) Basal skull fracture

This is more common than linear vault fracture after severe closed head injury and may involve the anterior and/or middle fossa. Anterior fossa fractures may initially result in bleeding into paranasal sinuses with epistaxis and later with CSF rhinorrhea. However, anterior fossa fractures may result in free communication between the paranasal sinuses and a dural tear without overt CSF rhinorrhea. The patient may therefore present days, weeks, or even years after head injury with meningitis without ever developing a CSF leak. Therefore a high index of suspicion is necessary in patients with severe closed head injury where epistaxis, periorbital bruising (so called ‘raccoon/panda eyes’) and extensive subconjunctival hemorrhage (Figure 4.18) occurs. Similarly, middle fossa fractures may or may not be associated with CSF otorrhea. Initially, the only clinical sign of fracture may be bleeding from the ear or bruising over the mastoid process (Battle’s sign; Figure 4.19). Fractures of the petrous bone may also cause deafness or a lower motor neuron facial nerve palsy. Again, a high index of suspicion of a CSF fistula is needed because, if present, these patients may later present with meningitis.

Figure 4.18  Anterior fossa fracture with bilateral ‘panda eyes’ (note subconjunctival hemorrhage).

Figure 4.19  Middle fossa fracture with Battle’s sign.

4.9.2 MENINGITIS

Whichever the portal of entry, with basal skull fractures organisms tend to be commensals from the paranasal sinuses or middle ear. Pneumococcal infection is therefore commonest, unless patients receive prophylactic antibiotics, which are more likely to encourage the overgrowth of resistant organisms. With vault fractures, staphylococci are the most likely organisms to cross the dura. Staphylococcal meningitis is also more likely to follow postoperative wound infection when a craniotomy has been performed, for example, for evacuation of a hematoma. Secondary infection may also occur with prolonged ventricular drainage. Meningitis may give rise to hydrocephalus, so that late deterioration in the level of consciousness with elevated ICP may occur some days after injury in a patient with very little primary brain damage. This again reinforces the usefulness of the concept of primary and secondary brain damage in the management of patients with head injury.

4.9.3 BRAIN ABSCESS

Post-traumatic brain abscess formation is generally rare and is almost always associated with a penetrating injury, particularly if there is in-driven foreign
material. It is extremely rare to develop a brain abscess following severe closed head injury unless there is fracturing of the posterior wall of the frontal sinus, although it may sometimes be impossible to detect that a penetrating injury has occurred. Such a case was seen several years after an apparently closed head injury. A frontal brain abscess was drained via craniotomy, and a non-radio-opaque wooden arrowhead was found within the abscess cavity. The fragment had entered unrecognized at the time of the original head injury. Although rare, such cases demonstrate that brain abscess may be a late complication of an apparently closed head injury.

4.10 Post-traumatic vascular damage

4.10.1 CAROTID AND MIDDLE CEREBRAL ARTERY (MCA) OCCLUSIONS

The internal carotid artery (ICA) may be damaged in the neck by acute flexion (Zelenock et al., 1982), extension (Stringer and Kelly, 1980) or directly by a safety belt, in which case a cutaneous abrasion over the cervical carotid artery is usually seen. These blunt injuries cause dissection of the intima with stenosis (Ueda et al., 1986), occlusion (Schultz et al., 1984) or thrombosis with distal embolization (Janon, 1970). Total occlusion of the internal carotid artery may lead to major hemisphere infarction that is visible on CT scan. The absence of flow in the internal carotid or the ipsilateral middle cerebral artery (MCA) may be detected with transcranial Doppler (TCD; Schneider et al., 1988). These patients may have relatively slight primary brain damage but a dense focal deficit (mimicking a stroke).

The ICA may also be damaged at the skull base by basal skull fractures (Aarabi and McQueen, 1978), in which case the patient may have associated severe primary brain damage and may therefore be comatose. The diagnosis of traumatic ICA occlusion is therefore more difficult in these cases, although it should be suggested by the characteristic infarct on CT or absent MCA flow on TCD.

Oclusion of intracranial arteries may also result from the herniations referred to above. These compress and occlude the anterior or posterior arteries. Survivors of such herniation may display a classical infarct in the vascular territory of that vessel (Figure 4.16). The intracranial ICA or MCA may become damaged with rapid acceleration or deceleration against the sharp sphenoid wing. Primary traumatic MCA occlusions are well recognized in young patients with closed head injury and may be associated with dissecting aneurysms (Kunze and Schiefer, 1971; Sato et al., 1971) and were more easily recognized in the pre-CT era, when angiography was used commonly in closed head injury.

4.10.2 TRAUMATIC SUBARACHNOID HEMORRHAGE

Traumatic subarachnoid hemorrhage (SAH) is known to be associated with cerebral vasospasm in more than 40% of cases (Macpherson and Graham, 1973) and with cerebral blood flow and TCD monitoring techniques the incidence of vasospasm was found to be 27% (Martin et al., 1992). Traumatic vasospasm following closed head injury is therefore an important cause of cerebral ischemia which is analogous to that found in spontaneous SAH.

4.10.3 ANEURYSMS

It may be difficult to differentiate a pre-existing aneurysm that ruptures as a result of trauma from a true post-traumatic aneurysm. Undoubtedly both types exist but it may be impossible to distinguish one from the other, although true post-traumatic aneurysms tend to be more common in the distal MCA (Fleischer et al., 1975). The true trauma-induced aneurysm may also enlarge (Bendoit and Wortzman, 1973) and is at risk of rupturing.

4.10.4 FISTULAE

Blunt injuries may lead to arteriovenous fistulae, which are usually associated with a cranial bruit. The commonest site is the carotid cavernous fistula, which often develops several days after the injury. It is characterized by proptosis with vasodilation of the sclera and may go on to cause SAH (Dohrmann et al., 1985). Fistulae may occur at other sites related to skull fractures (Feldman et al., 1980). They may also give rise to late SAH or even subdural hemorrhage in patients who otherwise have little or no primary brain damage.

4.11 Pyrexia following head injury

The development of pyrexia following head injury may be a sign of brain-stem damage. However the occurrence of pyrexia was one of the most significant predictors of mortality and morbidity in a series of 124 adult head-injured patients who were monitored continuously (minute by minute) in Edinburgh (Jones et al., 1994). There is also a revived interest in hypothermia as form of neuroprotection in head-injured patients: a multicenter prospective randomized controlled trial is currently under way in the USA, funded by the National Institute of Health.
86 PRIMARY AND SECONDARY BRAIN INJURY

4.12 Conclusion

While many classifications of brain damage are based on pathological findings, biochemical and radiological features, the importance of classifying brain damage clinically into primary and secondary types is that an understanding of the pathology will lead to more appropriate management. Most importantly, it helps non-specialists to understand the role of the prevention and treatment of brain swelling, hemorrhage and infection. It is important to teach medical students, nurses and doctors how to recognize primary and secondary brain damage. They may then be better able to prevent it from occurring in the first place or to minimize the effects once the cycle of secondary brain damage is initiated. In this way, through team cooperation, the gold standard of head injury management — eliminating secondary brain damage — may be reached.

4.13 References


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