The neuropathology of the vegetative state after an acute brain insult

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Summary
The vegetative state is often described clinically as loss of
function of the cortex while the function of the brainstem is
preserved. In an attempt to define the structural basis
of the vegetative state we have undertaken a detailed
neuropathological study of the brains of 49 patients who
remained vegetative until death, 1 month to 8 years after
an acute brain insult. Of these, 35 had sustained a blunt
head injury and 14 some type of acute non-traumatic
brain damage. In the traumatic cases the commonest
structural abnormalities identified were grades 2 and 3
diffuse axonal injury (25 cases, 71%). The thalamus was
abnormal in 28 cases (80%), and in 96% of the cases who
survived for more than 3 months. Other abnormalities
included ischaemic damage in the neocortex (13 cases,
37%) and intracranial haematoma (nine cases, 26%).
In the non-traumatic cases there was diffuse ischaemic
damage in the neocortex in nine cases (64%) and focal
damage in four (29%); the thalamus was abnormal in
every case. There were cases in both groups where the
cerebral cortex, the cerebellum and the brainstem were
of structurally normal appearance. In every case, however,
there was profound damage to the subcortical white
matter or to the major relay nuclei of the thalamus, or
both. These lesions render any structurally intact cortex
unable to function because connections between different
cortical areas via the thalamic nuclei are no longer
functional, and there is also extensive damage to afferent
and efferent cerebral connections.

Keywords: vegetative state; head injury; cerebral hypoxia

Abbreviations: DAI = diffuse axonal injury; TCI = total contusion index

Introduction
In the quarter of a century since Jennett and Plum described
and named the persistent vegetative state (Jennett and Plum,
1972), there has been continued and increasing interest in
the medical, ethical and legal aspects of the condition
(McLean, 1999). Its essential clinical features are loss of
any meaningful cognitive responsiveness, presumed lack of
awareness and therefore of consciousness, while there is
spontaneous breathing and a range of reflex responses as
well as periods of wakefulness (eyes open). It is often
described as loss of function in the cerebral cortex while
the function of the brainstem is preserved (Jennett, 1997).
Although the vegetative state may characterize the end-stage
of progressive dementing conditions in children and in adults,
most interest has focused on the vegetative state resulting
from an acute brain insult. Some such patients may recover
to a degree after having been diagnosed as being vegetative.
In the Multi-Society Task Force review of the world literature
(Multi-Society Task Force, 1994), half of the patients who
were vegetative at 1 month after a head injury had regained
consciousness after a year, as had one-third of those who
were vegetative for 3 months. The potential for recovery was
much less after non-traumatic insults. The Task Force, and
more recently the Royal College of Physicians of London
(Royal College of Physicians Working Party, 1996) have
therefore recommended that the vegetative state should not
be declared permanent until a year after a head injury, but
after 3 months following non-traumatic insults according
to the Task Force and after 6 months according to the
London report.

Neuropathologists have also been intrigued by the
vegetative state if only because, particularly in patients who
survive for only a few months, the brain may appear normal
or virtually so to the naked eye. Indeed, the underlying
structural changes responsible for the vegetative state may
be rather subtle to elucidate even with microscopy.

In the present paper we describe the neuropathological
findings in 49 patients who had remained in the vegetative state for more than 1 month after acute brain damage; in 35 cases the cause had been a blunt head injury and in the remaining 14 some type of hypoxic event.

Material and methods
The cases will be presented in two groups—those where the vegetative state was brought about by a head injury and those where there was another cause. Most of the cases have been taken from the records of the Department of Neuropathology of this Institute while six were kindly referred to us by Dr J. B. Brierley, lately of the MRC Laboratories near Carshalton. All had survived for at least 1 month after the acute event, as had all of the cases in the Multi-Society Task Force report (Multi-Society Task Force, 1994).

The clinical records available were reviewed by one of us (B.J.) in order to confirm that the patients had been vegetative at the time of death. Some of these records were from several years ago before recent diagnostic criteria were established. In certain cases some judgement was involved in deciding that the patient had been vegetative, but when there was doubt the case was rejected.

Group 1 (traumatic cases)
This consisted of 35 patients who had sustained a blunt head injury (Adams et al., 1999). There were 32 males and three females with an age range of 7–75 years (average 38 years). The cause of injury in 17 patients was a road traffic accident, in nine an assault, in six a fall and in three the precise circumstance of the head injury was not known. Eleven cases survived for less than 3 months, 11 for between 3 months and a year and 13 for more than a year. Particular attention was paid to whether or not the patient had talked after his injury (Reilly et al., 1975); if the patient had talked but had not been completely rational, the lucid interval was defined as being partial.

Group 2 (non-traumatic cases)
Of the 14 patients in this group, 11 were male and three were female. The age range was from 2 to 58 years (average 32 years). Survival was less than 3 months in six patients, between 3 months and a year in six and greater than a year in two. Five of the patients had experienced an intra-operative or postoperative cardiac arrest, three an acute episode of hypotension and two acute circulatory failure induced by drugs. There was one case of asphyxia, one of smoke inhalation, one of severe bronchospasm and one of severe intracranial infection.

Neuropathology
All brains were fixed in 10% formal saline for a minimum of 3 weeks prior to dissection, after which a full macroscopic and microscopic examination was undertaken in each case (Adams et al., 1980). After transecting the rostral brainstem, the cerebral hemispheres were cut into coronal sections 1 cm thick. The cerebellar hemispheres were cut at right angles to the folia and multiple horizontal sections were taken of the brainstem. In all but four cases, large bilateral blocks of the frontal, parietal, occipital and temporal lobes (three levels incorporating the basal ganglia and the hippocampal structures), each cerebellar hemisphere and the brainstem (three levels) were embedded in celloidin and sections stained with cresyl violet and by Heidenhain’s method for myelin. The remaining pieces of corpus callosum and brainstem were embedded in paraffin wax. In the four cases where celloidin studies were not undertaken, representative blocks were taken from all lobes of the cerebral hemispheres, the corpus callosum, the basal ganglia and the hippocampal structures (at least at two levels), the cerebellum (both hemispheres) and the brainstem (at least at three levels). Paraffin sections were routinely stained with haematoxylin and eosin and by the Luxol fast blue/cresyl violet technique. When considered appropriate, sections were stained by the Palmgren technique for axons and other stains including immunohistochemistry for astrocytes (GFAP, 1 : 3000; Dako, Ely, Cambs., UK) and macrophages (CD68, 1 : 200; Dako), which were developed with PAP or Vectastain ABC kit, respectively, and visualized with diaminobenzidine.

The severity of ischaemic brain damage was graded in both groups. In the traumatic cases it occurred mainly in the neocortex and was classified as severe when the lesions were diffuse or multifocal, or took the form of infarcts within specific arterial territories, and moderate when ischaemic damage was limited to arterial boundary zones, singly or in combination with subtotal infarction in the distribution of arterial territories (Graham et al., 1989). In the non-traumatic cases the ischaemic damage was always severe; it was graded either as diffuse when there was widespread neuronal loss throughout the affected structure, or focal when there were lines of demarcation between normal and abnormal tissue as, for example, with ischaemic damage in arterial boundary zones. The criterion of pressure necrosis in one or both parahippocampal gyri was used as evidence that the intracranial pressure had been high during life as a result of a supratentorial expanding lesion (Adams and Graham, 1976).

In the traumatic cases surface contusions were assessed semi-quantitatively using the total contusion index (TCI). This takes into account the depth and extent of the contusions in various parts of the brain: 0 means that there were no contusions, a contusion index of less than 9 is indicative of minimal contusions, while one of more than 37 is indicative of severe contusions (Adams et al., 1985b). Diffuse axonal injury (DAI) was graded and in this series most examples were of the more severe grades 2 and 3. In grade 3 there are focal lesions in the corpus callosum and in the dorsolateral segment(s) of the rostral brainstem and in grade 2 there is a focal lesion only in the corpus callosum. In grade 1, there is again axonal damage diffusely throughout the white matter,
but there are no focal lesions in the corpus callosum or in the brainstem (Adams et al., 1985a, 1989).

Only traumatic haematomas thought to be sufficiently large to act as significant intracranial expanding lesions (more than 35 ml) were recorded. The great majority of the haematomas so recorded had been evacuated surgically before death.

**Results**

**Group 1 (traumatic cases)**
The principal features are given in Table 1. Three of the patients had experienced a lucid interval—two total and one partial. All of the patients with lucid intervals had developed intracranial haematomas, one of whom had also sustained a postoperative cardiac arrest.

The most common structural abnormalities identified in the brains were grades 2 and 3 DAI (25 cases, 71%). Unlike the acute haemorrhagic lesions (Fig. 1) that are the characteristic focal features of DAI in patients who survive for only a short time after their injury, the lesions were shrunken, granular and sometimes cystic (Fig. 2). They often retained an orange-yellow colour because of the persistence of haemosiderin. They were not all visible macroscopically— in 15 of the 25 cases, one or both of the focal lesions were identifiable only microscopically (Table 1). With increasing survival the bulk of the white matter became reduced and there was enlargement of the ventricular system (Fig. 2A). Of the 10 patients without grades 2 or 3 DAI, seven had developed intracranial haematomas and nine had sustained moderate or severe ischaemic brain damage. There were also three cases of grade 1 DAI: in two of these there was, in addition, ischaemic damage in the cerebral cortex, and in one of these diffuse ischaemic damage in the thalamus also. In the third there was focal ischaemic damage in the thalamus.

Moderate or severe ischaemic brain damage was present in 15 (43%) of the traumatic cases. In six it was centred on arterial boundary zones in the cerebral hemispheres (Fig. 3), in four the ischaemic brain damage was diffuse, in two it affected specific arterial territories (Fig. 2A) and in one it was multifocal. In two there was diffuse neuronal loss in the thalamus without there being any neocortical damage. The intracranial pressure had been high in all but two of the patients who sustained ischaemic brain damage. In six of the 15 cases with ischaemic damage there was major extracranial injuries that might have contributed to an inadequate cerebral blood flow.

Intracranial haematomas had developed in nine (26%) of the cases—six subdural haematomas, one extradural haematoma and two cases with bilateral intracerebral haematomas. In all but one patient the intracranial pressure had been high and all the subdural and extradural haematomas had been evacuated during life.

The intracranial pressure had been high in 25 (71%) of the patients. Only eight of these had an intracranial haematoma.

In five cases (14%) there were abnormalities in the brainstem other than the focal lesions that are a feature of DAI. The intracranial pressure had been high in all of them. The lesions were in the midline in four cases and lateral (in a cerebral peduncle) in one. In all of these cases the lesions were small and non-haemorrhagic.

The TCI ranged from 0 to 21 (median 3.9), i.e. in not one case could contusions be classified as severe and in eight they were absent. If surface contusions are excluded, the neocortex was abnormal in only 13 of the cases and this took the form of ischaemic damage; this was diffuse in only four cases. There were no identifiable abnormalities in the cerebral cortex resulting from DAI.

The subcortical white matter was abnormally pale and granular in texture in 29 cases (83%), this being diffuse in all 28 patients with DAI. Focal damage to subcortical white matter was seen in two patients who had sustained ischaemic brain damage (Figs 2A and 3).

The thalamus was abnormal in 28 cases (80%), in 25 of which the damage was diffuse. This took the form of transneuronal change or ischaemic damage. In two of the cases with ischaemic damage there was no cortical ischaemic damage. In the other three cases there was focal infarction as a consequence of raised intracranial pressure and a compromised circulation through the posterior cerebral arteries or as part of the pattern of focal ischaemic brain damage. In DAI, retrograde thalamic degeneration occurs as a result of widespread axonal damage and takes some 3 months to develop. On the other hand, thalamic damage associated with ischaemia is apparent shortly after the hypoxic event. In DAI there is atrophy due to shrinkage of nerve cells and an astrocytosis in the lateral and ventral nuclei with relative sparing of the anterior and dorsomedial nuclei, the pulvinar, the centromedian nuclei and lateral geniculate bodies. In contrast, in cases in which the thalamic damage is attributable to ischaemia, there is neuronal loss and astrocytosis in the anterior and dorsomedial nuclei with relative sparing of the lateral and ventral nuclei. These two main patterns correspond to those described in cases of diffuse degeneration of the cerebral white matter in severe dementia after head injury (Strich, 1956) and in long survival after cardiac arrest (Brierley et al., 1971; Cole and Cowie, 1987).

There was a low incidence of fracture of the skull (12 cases, 34%). With the passage of time there was a trend for the brain weight to fall and for the ventricles to enlarge.

**Group 2 (non-traumatic cases)**
The structural abnormalities in these cases, given in Table 2, cover the spectrum of brain damage brought about by an acute hypoxic episode (Auer and Benveniste, 1997). The most common abnormality was diffuse damage in the neocortex (nine cases, 64%). This took the form of laminar necrosis, more severe in the depths of sulci than on their crests, and increasing in intensity from the frontal to the
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<td>NK</td>
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<td>M</td>
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<td>M</td>
<td>Assault</td>
<td>3 y</td>
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<td>No</td>
<td>1260</td>
<td>No</td>
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<td>32</td>
<td>15</td>
<td>M</td>
<td>RTA</td>
<td>3 y</td>
<td>No</td>
<td>No</td>
<td>1140</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
<td>No</td>
<td>++</td>
<td>C, D</td>
<td>No</td>
</tr>
<tr>
<td>33</td>
<td>8</td>
<td>M</td>
<td>Fall</td>
<td>4 y</td>
<td>T</td>
<td>Yes</td>
<td>670</td>
<td>EDHe</td>
<td>Yes</td>
<td>4</td>
<td>No</td>
<td>++</td>
<td>C, D</td>
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<td>M</td>
<td>RTA</td>
<td>6 y</td>
<td>No</td>
<td>No</td>
<td>1020</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>3 Mm</td>
<td>+</td>
<td>C, BZ</td>
<td>D</td>
</tr>
<tr>
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<td>42</td>
<td>M</td>
<td>Fall</td>
<td>8 y 6 m</td>
<td>No</td>
<td>No</td>
<td>1220</td>
<td>SDHe</td>
<td>Yes</td>
<td>14</td>
<td>3 Mm</td>
<td>+</td>
<td>C</td>
<td>BZ</td>
</tr>
</tbody>
</table>

**Table 1 Traumatic cases.** The principal clinical and neuropathological features in 35 patients who survived in a vegetative state for 1 month or more after a head injury.

*Cause: RTA = road traffic accident. Survival: w = week(s); m = month(s); y = year(s). Lucid: T = totally lucid immediately after injury; P = partially lucid; NK = not known. Brain weight: NK = not known. Intracranial haematoma: SDH = subdural haematoma; EDH = extradural haematoma; ICH = intracerebral haematoma; e = evacuated. ICP+ = raised intracranial pressure. TCI = total contusion index. DAI = diffuse axonal injury: 1, 2, 3 indicate grade; m = focal lesions seen only microscopically; M = focal lesions seen macroscopically; Mm = one lesion seen macroscopically, the other only microscopically; IB = ischaemic brain damage in cerebral cortex; + = moderate; ++ = severe. Neocortex: BZ = ischaemic brain damage in arterial boundary zones; AT = ischaemic brain damage in arterial territories; D = diffuse damage; F = focal damage. Brainstem: M = focal damage in midline; L = lateral damage. Hydrocephalus: + = slight enlargement of the ventricular system; ++ = moderate; +++ = severe.*
occipital poles often with selective sparing of the calcarine cortex. With the passage of time the affected cortex became rather granular and shrunken, there was a reduction in the bulk of the white matter and there was ventricular enlargement (Fig. 4). In three cases the ischaemic damage was restricted to arterial boundary zones of the type known to be associated with an acute episode of hypotension (Adams et al., 1966).

In the one case with ischaemic damage in more than one arterial territory, there had been an intracranial expanding lesion in the form of an abscess in the left frontal lobe brought about by a localized penetrating head injury that had initially not caused a disturbance of consciousness. As can be seen from Table 2, there were variable abnormalities in the caudate nucleus, the putamen, the globus pallidus and the cerebellum, but in every case there was profound diffuse neuronal loss in each thalamus and hippocampus. In eight cases there were variable minor abnormalities in the brainstem, the most common being focal changes in the substantia nigra or in some of the major motor nuclei. In none of the cases was there histological evidence to suggest that the intracranial pressure had been high (Adams and Graham, 1976).

There was only one case in which the neocortex was structurally of normal appearance (case 12). This patient had been accidentally incarcerated in a hermetically sealed motorized vehicle and there was a possibility that there had been carbon monoxide in the atmosphere. The most dramatic abnormality was extensive damage to the subcortical white matter associated with widespread destruction of axons and loss of myelin, and reactive changes in astrocytes and microglia. In this patient there were also diffuse abnormalities in the thalami and in the hippocampi.

As with the patients in group 1, there was a trend for the brain weight to decrease and for the ventricles to enlarge as survival increased.
Discussion

There have in the past been many reports of disorders of consciousness after acute brain insults, usually of hypoxic causation (French, 1952; Adams et al., 1966; Brierley et al., 1971; Ingvar et al., 1978; Dougherty et al., 1981; Cole and Cowie, 1987; Relkin et al., 1990). Very few publications, however, have specifically addressed the underlying basis of the persistent vegetative state. An exception is the review of the literature by Kinney and Samuels of cases of the vegetative state of traumatic and non-traumatic causation (Kinney and Samuels, 1994). Precise clinical details and duration of survival were not defined in this review and not all of the cases would be accepted as being vegetative using current criteria. They concluded, however, that the vegetative state results from widespread and bilateral damage to (i) the cerebral cortex itself; (ii) the thalamus; or (iii) many of the intra- and subcortical connections (via axonal injury and/or demyelination of the cerebral hemispheric white matter). They present three diagrams: one with diffuse destruction of the cerebral cortex only, one with diffuse damage to the subcortical white matter only and one with diffuse damage to each thalamus only. We have never seen a case in which there was diffuse hypoxic damage to the cerebral cortex without there being correspondingly severe damage in each thalamus. Kinney and colleagues reported a single case of the vegetative state in a young woman who survived for 10 years after cardiopulmonary arrest (Kinney et al., 1994). In this patient the damage to the cerebral cortex was in the parasagittal regions, i.e. in arterial boundary zones, and much of the neocortex was spared. There was, however, severe bilateral thalamic damage and they suggested that this may sometimes be more important than cortical damage in the production of the vegetative state. A similar case has been reported by Jellinger (Jellinger, 1994).

The concept that axons may be damaged directly at the time of a head injury has a long and chequered history. Strich was the first to suggest that it could be an important factor when she described the neuropathological findings in a series of cases with ‘severe post-traumatic dementia’ in which there was widespread Wallerian-type degeneration in subcortical white matter and in descending tracts in the brainstem and spinal cord (Strich, 1956). She was of the opinion that there had been disruption of axons at the time of injury brought about by shearing strains. In support of this view was the work of Holbourn (Holbourn, 1943, 1945) and of Pudenz and Shelden (Pudenz and Shelden, 1946) on shearing injury and the fact that in patients with this type of brain damage there are gross and permanent neurological abnormalities from the moment of injury. The observations of Strich and her opinion as to the pathogenesis of axonal damage were also supported by Peerless and Rewcastle (Peerless and Rewcastle, 1967) and by Zimmerman and colleagues (Zimmerman et al., 1978), both groups describing examples of shearing injury, and by ourselves (Adams et al., 1977) in an account of 19 patients found post-mortem to have ‘diffuse damage to white matter of immediate impact type’. Others, however, were of the opinion that the damage to axons was secondary to factors such as hypoxia and ischaemia, brain swelling, or damage to the brainstem secondary to a high intracranial pressure brought about by an intracranial expanding lesion (Jellinger and Seitelberger, 1970; Jellinger, 1977; Peters and Rothemund, 1977).

The final proof that axons could be damaged at the time of a head injury came about as a result of experimental studies in non-human primates when it was shown that axonal damage identical to the type already known to occur in man could be produced by non-impact angular acceleration of the head (Adams et al., 1982; Gennarelli et al., 1982). At that time we introduced the term ‘diffuse axonal injury’, now the internationally accepted term (Gennarelli et al., 1998) to describe this type of brain damage resulting from a head injury. On the basis of this controlled experimental model, three grades of severity of DAI were defined and were applied to man (Adams et al., 1989). In the most severe form (grade 3) there are, in addition to microscopical evidence of widespread damage to axons in all parts of the brain, focal lesions in the corpus callosum and in the dorsolateral sector(s) of the rostral brainstem. In grade 2 there is a focal lesion only in the corpus callosum, while in grade 1 there are no focal lesions (Adams et al., 1989). There were three cases with grade 1 DAI in the present series and in all three there was also ischaemic brain damage; this grade of DAI may be a cause of persistent disability after a head injury (B. Jennett, personal communication), but, on its own, does not appear to be a cause of the vegetative state.

The focal lesions of DAI can often be seen macroscopically, but sometimes only on microscopic examination. In earlier studies the identification of axonal injury was dependent on silver staining techniques to identify axonal swellings (the ‘retraction’ balls of Cajal), but more recently immunohistochemical methodology using an antibody to the precursor
Table 2: Non-traumatic cases. The principal clinical and neuropathological features in 14 patients who survived in a vegetative state for more than 4 weeks after an acute non-traumatic cerebral insult.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Cause</th>
<th>Survival</th>
<th>Brain weight (g)</th>
<th>ICP+</th>
<th>Hydrocephalus</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neocortex</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>Post-op. CA</td>
<td>4 w</td>
<td>1375</td>
<td>No</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>M</td>
<td>Intra-op. CA</td>
<td>4 w</td>
<td>1250</td>
<td>No</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>M</td>
<td>Intracranial infection: convulsion; hypot.</td>
<td>8 w</td>
<td>1420</td>
<td>No</td>
<td>++</td>
<td>BZ</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>Post-op. CA</td>
<td>8 w</td>
<td>1200</td>
<td>No</td>
<td>No</td>
<td>BZ</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>M</td>
<td>Drugs/alcohol: hypot.</td>
<td>10 w</td>
<td>1300</td>
<td>No</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>F</td>
<td>Cardiomyopathy (pregnancy): hypot.</td>
<td>11 w</td>
<td>1320</td>
<td>No</td>
<td>+</td>
<td>BZ</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>M</td>
<td>Cerebral abscess/ meningitis</td>
<td>4 m</td>
<td>1420</td>
<td>No</td>
<td>++</td>
<td>AT</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>M</td>
<td>Bromsulphthalein CA</td>
<td>5 m</td>
<td>1250</td>
<td>No</td>
<td>+++</td>
<td>D</td>
</tr>
<tr>
<td>9</td>
<td>58</td>
<td>M</td>
<td>Bronchospasm CA</td>
<td>5 m</td>
<td>1100</td>
<td>No</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>M</td>
<td>Smoke inhalation</td>
<td>7 m</td>
<td>1110</td>
<td>No</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>M</td>
<td>Post-op. CA</td>
<td>9 m</td>
<td>NK</td>
<td>No</td>
<td>+++</td>
<td>D</td>
</tr>
<tr>
<td>12</td>
<td>21</td>
<td>M</td>
<td>Asphyxia – sealed vehicle (?CO)</td>
<td>10 m</td>
<td>1460</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>M</td>
<td>Stab wound: hypot., convulsions Post-op. CA</td>
<td>1 y 9 m</td>
<td>1050</td>
<td>No</td>
<td>++</td>
<td>D</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>F</td>
<td></td>
<td>4 y</td>
<td>515</td>
<td>No</td>
<td>+++</td>
<td>D</td>
</tr>
</tbody>
</table>

Cause: CA = cardiac arrest; hypot. = an acute episode of hypotension; CO = possible presence of carbon monoxide. Survival: w = week(s); m = month(s); y = year(s). Brain weight: NK = not known. ICP+ = raised intracranial pressure. Hydrocephalus: + = slight enlargement of the ventricular system; ++ = moderate; +++ = severe. Neocortex: D = diffuse hypoxic damage; BZ = hypoxic damage in arterial boundary zones; AT = hypoxic damage in arterial territories. SCWM = subcortical white matter; F = focal damage in relation to damage to the neocortex; A = astrocytosis; DLM = diffuse loss of myelin. In all other columns: D = diffuse hypoxic damage; F = focal damage; BZ = damage in arterial boundary zones; m = minimal abnormalities identified only microscopically.
protein of β-amyloid has rendered the identification of axonal injury much more reliable (Gentleman et al., 1993; Sherriff et al., 1994). Indeed, it would now appear that grade 1 DAI is of frequent occurrence in head injuries (Gentleman et al., 1995). There is now, as a result of these more recent studies, a structural basis to account for persisting minimal clinical sequelae after what appeared to have been only a minor head injury (Oppenheimer, 1968; Clark, 1974; Blumbergs et al., 1994).

Whether or not there is total disruption of axons at the moment of injury, as had originally been suggested by Strich (Strich, 1956) and subsequently supported by other investigators, has been controversial. In ultrastructural studies of the brains of non-human primates subjected to shear-strains identical to those known to produce DAI in the brain, disruption immediately after injury has been seen (Maxwell et al., 1993). Such primary axotomy, however, is uncommon and there is increasing recognition of damaged axons undergoing a process of secondary axotomy (Maxwell et al., 1997). The axons undergo a sequence of events: initially there is focal swelling of axons (Maxwell et al., 1995; Pettus and Povlishock, 1996) and thereafter swelling of axonal mitochondria (Pettus et al., 1994; Maxwell et al., 1995; Pettus and Povlishock, 1996), the development of nodal blebs (Maxwell et al., 1991) and/or a focal decrease in the internodal axonal diameter. This is followed by loss of axonal microtubules (Maxwell, 1995; Pettus and Povlishock, 1996; Jafari et al., 1997; Povlishock et al., 1997) and alterations of the intra-axonal relationships of neurofilaments (Pettus and Povlishock, 1996; Jafari et al., 1997). Next, there is involution of the internodal axolemma (Povlishock, 1992; Pettus et al., 1994; Maxwell et al., 1995) followed by separation of the axolemma from the internal aspect of the myelin sheath (Maxwell et al., 1995), the development of axonal swellings (Maxwell et al., 1991, 1995; Povlishock, 1992), the development of myelin intrusions (Povlishock et al., 1983; Maxwell et al., 1995) and finally axonal separation (Povlishock, 1992; Jafari et al., 1997) to form axonal (‘retraction’) bulbs. Subsequently, more severe morphological changes take place including axonal rupture and Wallerian-type degeneration (Strich, 1956). This has led to the concept of secondary axotomy in the pathogenesis of DAI. In a review of the literature, Maxwell and colleagues concluded that, whereas primary axotomy could be identified within 60 min of injury, secondary axotomy required a minimum of 4 h to develop (Maxwell et al., 1997).

Whether or not axons are disrupted at the moment of injury in patients who sustain DAI, they are clearly rendered immediately dysfunctional and temporary changes of conduction in damaged axons now seem the most likely cause of transient disturbances of consciousness after a head injury (concussion). Further clinicopathological studies have established that there are many differences between patients with the more severe grades of DAI compared with other types of head injury. For example, the former never experience a lucid interval; they have a low incidence of fracture of the skull, traumatic intracranial haematomas and increased intracranial pressure; and surface contusions are seldom severe—all features of the present series (Table 1).

The occurrence of structural changes in the thalamus in association with DAI is dependent on the length of survival of the patient because it is transneuronal in origin and takes about 3 months to appear. Thus, in the present series the thalamus appeared normal on microscopical examination in six of the seven patients with DAI who survived for 12 weeks or less after their injuries, notwithstanding the presence of widespread damage to subcortical white matter (Table 1). There is no rational explanation for the fact that there was no transneuronal change in the thalamus of traumatic case 25 who survived in a vegetative state for 18 months as a result of DAI despite there being diffuse degeneration in the subcortical white matter. This was the only patient in the traumatic group who survived for 3 months or more in whom there were no identifiable abnormalities in the thalamus. In the traumatic group the thalamus was abnormal in 28 (80%) of all cases and in 96% of those who survived for more than 3 months.

The importance of grades 2 and 3 DAI as a cause of the vegetative state after head injury is evident from Table 1, these being a feature of 71% of the cases in the present series.

Moderate to severe ischaemic brain damage, particularly in the patients with intracranial haematomas or extracranial injuries, was also common (43%). It has long been known that ischaemic damage is not uncommon in patients with fatal head injuries (Graham et al., 1978), particularly if the intracranial pressure has been high (Graham et al., 1987, 1989). In the series of 151 unselected non-missile head injuries published by Graham and colleagues, moderate to severe ischaemic brain damage was observed in 96 cases (64%) (Graham et al., 1978). Its pathogenesis, namely a regional or global failure of cerebral blood flow, is likely to
be similar to the cause of the brain damage in some of the non-traumatic cases to be discussed in the next section.

A striking feature in the traumatic cases of the vegetative state is the low incidence of damage to the brainstem (14%); in all five cases with this type of brain damage it was slight and never haemorrhagic. This confirms the view we have held for a long time that patients who develop classic secondary haemorrhage and infarction in the brainstem as a result of an acute intracranial expanding lesion survive for only a short time. Thus, a post-traumatic vegetative state may occur in patients in whom both the cerebral cortex and brainstem are intact.

The causes and patterns of hypoxic brain damage in patients who have sustained an acute circulatory catastrophe have long been an interest of neuropathologists and clinicians (Adams et al., 1966; Dougherty et al., 1981; Cole and Cowie, 1987; Kinney and Samuels, 1994). The classic example is the brain damage brought about by a period of true cardiac arrest. This takes the form of diffuse neuronal necrosis in the regions of selective vulnerability. In the neocortex there is laminar necrosis, more severe in the depths of sulci than on their crests, and tending to increase in severity from the frontal to the occipital poles, but often with some sparing of the medial occipital cortex. There is also diffuse neuronal necrosis in the hippocampal and amygdaloid structures, in the major relay nuclei of the thalamus, in the Purkinje cells of the cerebellum and, variably, in other structures in the deep grey matter. Essentially similar patterns of brain damage may occur as a result of other types of hypoxic insult such as status epilepticus, carbon monoxide poisoning and asphyxia (Auer and Benveniste, 1997), and hypoglycaemia (Auer et al., 1989). This diffuse pattern of ischaemic damage was found in nine of the cases of the non-traumatic vegetative state (Table 2). The second pattern of brain damage is focal. Here the classic example is brain damage brought about by a short episode of profound hypotension (Adams et al., 1966; Torvik and Jorgensen, 1969; Auer and Benveniste, 1997) when ischaemic damage is confined to the arterial boundary zones in the cerebral and cerebellar hemispheres. The affected zones tend to be wedge-shaped with their base on the surface and their apex deep within the brain, e.g. adjacent to the angle of a lateral ventricle. There is almost always involvement of the thalamus and there is variable involvement of the hippocampal structures and the deep grey matter. This pattern of brain damage was present in three of the non-traumatic cases (Table 2). Another type of focal ischaemic brain damage is, because of local factors compromising the blood flow through individual arteries, restricted to specific arterial territories. There was one case of this type in the present series; there were also variable ischaemic lesions in other structures, but damage to the thalamus was diffuse (Table 2).

In one case (case 12 in Table 2) there were no abnormalities in the cerebral cortex, the principal abnormality being severe destruction of the subcortical white matter of the type associated with carbon monoxide poisoning (Lapresle and Fardeau, 1966; Vuia, 1967; Auer and Benveniste, 1997), and
there was the unconfirmed possibility that there could have been some carbon monoxide in the vehicle in which he had become accidentally sealed. An almost identical case of confirmed carbon monoxide poisoning (Fig. 5) that we have reported (Hart et al., 1988) would have been included in this paper had the patient survived in a vegetative state for the additional few days required to fulfil the criterion of a month’s survival. In both cases, there was diffuse neuronal loss in the thalamus. It is of some interest that we have never seen or encountered a case of the vegetative state caused by hypoglycaemia. It would appear, therefore, that most such cases either die less than a month after the episode or make varying degrees of recovery. However, one of us (B.J.) has seen a clinical case of a teenager who survived for several years in a vegetative state after hypoglycaemia. Some certainly remain severely disabled (Kalimo and Olsson, 1980; Auer et al., 1989).

In patients who sustain severe brain damage as a result of some catastrophic circulatory event, there is characteristically minimal or no damage in the brainstem, as was the case in the present series.

Thus, as in the traumatic group of cases, there are patients in the non-traumatic group where the vegetative state was present without there being diffuse damage to the cerebral cortex or severe damage in the brainstem. Diffuse neuronal loss in the thalamus was, however, a common factor in all.

The Multi-Society Task Force recognized that the potential for recovery from the vegetative state was greater after traumatic than non-traumatic insults (Multi-Society Task Force, 1994). This may be related to the differing types of damage sustained by neurons in the thalamus. In acute hypoxic episodes the neurons that are lost have undergone ischaemic necrosis and will therefore never function again.

In contrast, in DAI there is no actual loss of neurons, only transneuronal degeneration. If there is any delayed restoration of function in the axons damaged at the time of the original injury, the substrate of thalamic neurons is still there and, conceivably, may be able to function again. Another difference between the traumatic and non-traumatic cases was the frequency of diffuse ischaemic damage in the neocortex: this occurred in 64% of the non-traumatic cases but in only 11% of the traumatic cases. The respective figures for any type of ischaemic damage in the neocortex were 93 and 37%.

We also have considerable experience of the neuropathological abnormalities in patients who remained severely disabled but not vegetative as a result of an acute brain insult. In some of these brains there were lesions similar to those found in some of the vegetative patients, particularly in the traumatic group, in that some severely disabled patients had grades 2 or 3 DAI including damage to the thalamus. The severity of the damage may have been more severe in the vegetative patients but, as yet, we have been unable to devise a quantitative method to measure damage to axons.

It is clear from the present account of 49 clinically confirmed patients who were in a vegetative state for 1 month or more, that this condition can occur in patients in whom there are no identifiable structural abnormalities in the cerebral cortex, the cerebellum or the brainstem. The features common to all are widespread destruction of the white matter of the cerebral hemispheres and/or the thalamus. With one exception (case 25)—and we cannot account for this—all of the patients with DAI in whom no abnormalities could be identified in the thalamus had not survived long enough for transneuronal degeneration to have occurred. Diffuse damage to subcortical white matter was, however, common to all patients. In all of the patients in whom the vegetative state had been produced by some hypoxic episode, there was diffuse and severe damage to each thalamus. It must therefore be concluded that the fundamental structural abnormality in patients with the vegetative state is subcortical and is related to damage to the white matter of the cerebral hemispheres and/or the thalamus. These lesions do, however, render any structurally intact cortex unable to function because connections between different cortical areas via the thalamic nuclei are no longer viable, and there is also extensive damage to afferent and efferent cerebral connections.

References


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