THE NEUROPATHOLOGICAL BASIS OF A POOR OUTCOME AFTER NON-MISSILE HEAD INJURY

by

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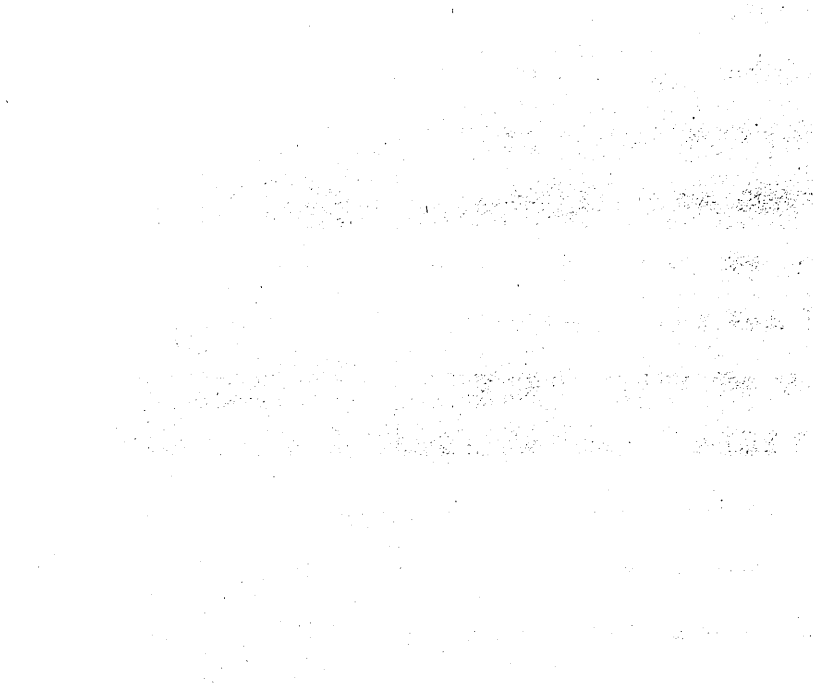

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SUMMARY OF THESIS

The main purpose of this thesis was to identify the pathological processes underlying a poor outcome after non-missile head injury. To achieve this, comprehensive neuropathological studies were undertaken in a postmortem series of 48 fatal cases of non-missile head injury who had survived more than one month and were classified as comatose, vegetative or severely disabled. There had been a fracture of the skull in 26 cases (54%). Cerebral contusions were present in 43 cases (90%). Contusions were quantified by the "contusion index" method and their anatomical distribution and relationship to other lesions examined. Intracranial haematomas had been present in 26 cases (54%) and had been evacuated neurosurgically in 21 cases (44%). Diffuse axonal injury was present in 25 cases (52%) and was the most common finding apart from cerebral contusions. Focal lesions in the corpus callosum and rostral brain stem occurring in cases of diffuse axonal injury were analysed and formed the basis of a method for grading the severity of diffuse axonal injury. Diffuse axonal injury was shown to be associated with various lesions apparently of vascular origin, including sulcal infarcts, gliding contusions and other parenchymal lesions. It is suggested that these features are manifestations of "diffuse vascular injury". There was evidence of a previously high intracranial pressure, in the form of pressure necrosis in one or both parahippocampal gyri, in 28 cases (58%). Lesions in the brain stem due to a high intracranial pressure were considered

to be present in 14 cases (29%). In 8 of these the lesions were large and took the form of a haematoma or infarcts. In the other 6 cases, however, the secondary lesions could only be detected microscopically and comprised minute infarcts or foci of gliosis. Brain damage of hypoxic or ischaemic origin was present in 27 cases (56%). This was diffuse in 2 cases, of boundary-zone distribution in 5 cases, and occurred within main arterial territories or in the region of the basal ganglia in the remaining 20 cases.

Diffuse axonal injury, cerebral contusions, hypoxic/ ischaemic brain damage and secondary lesions in the brain stem were thus identified as the principal types of structural damage. There was considerable overlap since there was more than one type of lesion in 40 cases. One type of lesion only was found in 8 cases, but in no case was a secondary lesion in the brain stem the only type of lesion present. Four main categories of structural damage were identified as contributing most to the clinical outcome. These were: diffuse axonal injury in 25 cases (52%); hypoxic/ ischaemic brain damage in 11 cases (23%); a combination of a macroscopic secondary lesion in the brain stem and hypoxic/ ischaemic brain damage in 8 cases (17%); and, cerebral contusions in 4 cases (8%). There was a relationship between the grade of diffuse axonal injury and the clinical outcome. Diffuse axonal injury was the most frequent cause of a vegetative state (68% of cases). A macroscopic secondary lesion in the brain stem together with hypoxic/ischaemic brain damage was the most common finding in

cases of prolonged coma (50% of cases), and hypoxic/ischaemic brain damage was the most common cause of severe disability (44% of cases). Diffuse axonal injury was the next most frequent cause of both prolonged coma (33% of cases) and severe disability (38% of cases). Diffuse axonal injury was thus found to be the most common cause of a poor outcome after non-missile head injury.

Ventricular enlargement was quantified by a point-counting method. Hydrocephalus was deemed to be present in 65% of cases assessed. In general there was a relationship between the size of the ventricles and duration of survival. Apart from one patient of long survival who died as a result of a cerebellar haematoma, a definite cause of obstructive hydrocephalus or evidence of a terminally high intracranial pressure was not found in any case although one patient had been treated clinically for obstructive hydrocephalus. Cerebral atrophy appeared to be the most important factor leading to ventricular dilatation.

Some complications of late onset were identified. These comprised cerebrovascular disease, central pontine myelinolysis associated with Marchiafava-Bignami disease, and pellagra.

CHAPTER 1.

INTRODUCTION

Many patients who survive a severe head injury fail to make a good recovery even if they regain consciousness. In the United Kingdom, "major persisting handicap" due to head injury is said to have a prevalence of 150 cases per 100,000 of the population (Lancet, 1983), while the incidence of "permanent disability" has been estimated as 1,500 new cases per annum (Lewin, 1970) including some 400 patients who remain "unconscious" for a month or longer (Lewin, 1968). The main purpose of this thesis is to identify the pathological processes underlying a poor outcome after non-missile head injury.

Clinical aspects

Before turning to the pathological literature, it may be useful to consider some clinical aspects of post-traumatic brain damage.

The Glasgow Outcome Scale was devised by Jennett and Bond (1975) to meet the need for a more objective assessment of recovery after head injury. Apart from death, the Scale comprises four categories: vegetative state; severe disability; moderate disability; and, good recovery. The worst outcome is the vegetative state, considered to be worse even than death for both patients and their relatives (Jennett, 1976). The term vegetative state has tended to replace the older expression persistent vegetative state which was introduced by

Jennett and Plum (1972) to describe patients who "recover" from coma yet remain profoundly unresponsive and only capable of primitive postural and reflex movements. Respiration is spontaneous, so these patients are not "brain-dead" (Medical Royal Colleges, 1976). Sleep-waking cycles are maintained, and when awake, patients may appear to look at, and even follow with their eyes, visual or auditory stimuli. This apparent alertness is belied by the complete absence of a voluntary response to any stimulus.

The terms vegetative state or persistent vegetative state recall the earlier vie végétative (Arnaud et al., 1963) and vegetative survival (Vapalahti and Troupp, 1971), but the literature abounds with other names, for identical or similar conditions, which have been criticised by Jennett and Plum (1972) either because they presume an anatomical level for the underlying lesion, e.g. apallic syndrome (Kretschmer, 1940; Dalle Ore et al., 1977), chronic brainstem syndrome (quoted by Jennett and Plum, 1972), or because they are ambiguous or imprecise with regard to the neurological state, e.g. prolonged unconsciousness (French, 1952), coma prolongé (Le Beau et al., 1958), coma vigile (Alajouanine, 1957), and severe post-traumatic dementia (Strich, 1956). Terms which incorporate the idea of "coma" seem to be particularly inappropriate since a distinction can be made between the vegetative state and coma, the latter being a sleep-like condition which can be defined as "not opening eyes, not obeying commands and not uttering words" (Teasdale and Jennett, 1976; Jennett and Teasdale, 1977).

Unlike the vegetative state, it is unusual for coma to persist for more than a few weeks.

Severe disability on the Glasgow Outcome Scale indicates a patient who is conscious but dependent on another individual for daily living. Moderate disability denotes a patient who is disabled but independent in daily life and able to work. Good recovery is considered to have occurred when normal occupational and social activities have been resumed.

Use of the Glasgow Outcome Scale has made a major contribution to understanding the nature of disability and the process of recovery after head injury. Analysis of a series of 593 patients with severe head injury (i.e. in coma for at least six hours) showed that the outcome at six months was as follows (Jennett et al., 1977a):

Death	48%
Vegetative State	2%
Severe Disability	10%
Moderate Disability	18%
Good Recovery	23%

In patients better than vegetative, mental abnormality tends to contribute more than physical disability to overall handicap (Jennett et al., 1981). Recovery is a dynamic process, but most improvement takes place in the first three to six months after injury. Those still vegetative at three months will not achieve independence, while as many as 50 per cent of patients vegetative one month after injury will die within the following year (Braakman, 1984). On the other hand, some vegetative

patients will remain alive for many years without any change in their neurological state (Bethlem, 1968).

Review of pathological literature

Some patients may therefore survive the acute episode only to become vegetative or severely disabled, perhaps without any further recovery before death supervenes. What is the cause of such profound neurological disturbance? These patients, as the above figures suggest, are not common. In many cases the length of survival ensures that death occurs in institutions for long term care where there is little interest in obtaining post-mortem examinations. Although the first report of the findings in a (probable) vegetative patient was that of Rosenblath (1899), it was not until the Second World War that improvements in intensive care enabled severely brain damaged patients to live long enough in sufficient numbers to allow a greater appreciation of the factors underlying the neurological outcome. Nevertheless, clinico-pathological studies are few and tend to be confined to small series or individual cases. More importantly, there are fundamental disagreements, not only as to the type of the basic lesion, but also about whether the brain damage is "primary" (i.e. occurring at the moment of impact) or "secondary" (i.e. developing as a later complication).

Thus, some consider diffuse damage to white matter to be the most important lesion. This was first observed by Rosenblath (1899) in the brain of a tight-rope walker who had remained "unconscious" for eight months after falling from a trapeze.

Rosenblath attributed immense loss of nerve fibres and widespread degeneration of white matter to the effects of concussion at the time of the injury. Sixty-six years later, Strich (1956) described a series of five patients (survival 142 to 456 days) with what she called "severe post-traumatic dementia". Using the Marchi technique, Strich was able to demonstrate extensive Wallerian degeneration in the white matter of the cerebral hemispheres, cerebellum, brain stem and spinal cord, and adduced evidence that this was the result of physical damage to nerve fibres at the time of injury. Dechaume et al. (1962) showed that extensive demyelination was the most constant and striking feature in the brains of five patients in "prolonged coma" (survival 65 - 158 days). Similar observations were made in individual cases by Osetowska (1964) (survival 2.5 years) and Bethlem (1968) (survival 10 years). Osetowska considered that the demyelination, which she called "leuco-encéphalopathie oedemateuse post-traumatique", was a toxic effect of post-traumatic cerebral oedema.

Other authors, however, have championed the role of focal lesions in the brain stem as the cause of post-traumatic neurological disturbance. Thus, French (1952) identified infarcts in the brain stem as the cause of "prolonged unconsciousness" in a series which included two cases of head injury (survival 7 and 9 months). Jellinger and Seitelberger have consistently emphasised both the frequency and clinical importance of focal lesions in the brain stem of patients with "protracted post-traumatic encephalopathy". Their expanding

series most recently comprised as many as 100 cases (survival 21 - 900 days) variously described in successive papers as "comatose", "post-comatose", "apallic" and "vegetative" (Jellinger, 1965; Jellinger and Seitelberger, 1969, 1970; Seitelberger and Jellinger, 1971; Jellinger, 1977, 1983). These authors have demonstrated the complexity of the pathological processes involved and drawn attention to the frequency of both focal and diffuse lesions in the cerebral hemispheres and brain stem. Their main conclusions, although reiterated in subsequent articles, were most clearly stated by Jellinger and Seitelberger (1970) as follows: brain-stem lesions are more frequent than any other type of damage; in none of their cases could "coma vigile" be attributed to diffuse degeneration of white matter alone, while all were associated with damage to the diencephalon and brain stem; the presence or absence of lesions in the brain stem and their specific pattern of distribution preferentially account for the prognosis of head injuries. The majority of these brain-stem lesions were stated to be secondary to raised intracranial pressure (Jellinger and Seitelberger, 1970; Jellinger, 1977, 1983). Peters and Rothemund (1977) arrived at the same conclusion regarding the significance of secondary brain-stem lesions in their study of 20 "apallic" patients (survival 3 weeks - 7 years). Crompton, Teare and Bowen (1966) also, while conceding that diffuse degeneration of white matter is the basis of "post-traumatic dementia" and also a common finding in "prolonged coma", nevertheless identified focal lesions, including regions of ischaemic

necrosis between the subthalamic region and the pons as the cause of "prolonged coma" in their series of nine patients (survival 2 weeks - 14 months).

Zoltán (1966) carried out a study to investigate whether lesions of the brain stem alone were responsible for "vigil coma" in a series of eight patients (survival 24- 420 days). In seven cases there were microscopic foci of softening in the brain stem, while in the eighth case there was atrophy of the pons associated with Wallerian degeneration. In all cases, however, there was also cortical damage comprising both contusional and hypoxic damage. Zoltán concluded that unconsciousness in these patients was due to the combination of diffuse cortical damage of mixed aetiology with a brain-stem lesion, rather than a lesion in the brain stem alone.

The vegetative state is not confined to survivors after head injury but has other causes (Jennett and Plum, 1972; Higashi et al., 1977), notably diffuse hypoxic brain damage of the type found, for example, after cardiac arrest (Brierley et al., 1971). Ischaemic brain damage is common in fatal head injuries generally. Graham et al. (1978) found ischaemic damage (all types) in 91 per cent of a series of 151 cases. This was graded as "severe" in 19 per cent including 8 cases (53 per cent) with diffuse hypoxic damage. In view of this, hypoxic/ischaemic brain damage might be expected to be an important cause of not only the vegetative state, but also lesser degrees of disability after head injury. There is, however, a dearth of information on this point. Denst et al. (1958) described diffuse

degeneration of the cerebral grey matter in a patient who survived "akinetic and mute" for 10 months, although they attributed this lesion to trauma rather than hypoxia. Zoltán (1965), quoted above, may have been alluding to diffuse hypoxic damage in his cases. Jellinger (1977), however, found diffuse hypoxic brain damage in only 7 cases (8.8 per cent) out of a series of 80 "apallic" patients.

From the foregoing review, three lesions would appear to be of importance in determining the outcome of patients who survive more than a few weeks after injury, namely, diffuse damage to white matter, focal lesions in the brain stem and hypoxic/ischaemic brain damage. In view of the lack of unanimity over the pathological basis of severe neurological disturbance, and the probability that lesions will vary from case to case and will also occur in different combinations, published data on the frequency of different lesions may be of limited value. Strich (1956) suggested that diffuse white matter damage was present in about one-third of a group of patients surviving more than 6 weeks after injury. Jellinger (1977) found brain-stem lesions in 86.3 per cent, diffuse damage to white matter in 62.5 per cent and diffuse hypoxic brain damage in 8.8 per cent. These findings contrast with those of Adams et al. (1980a) who, in a consecutive series of 151 fatal head injuries (survival 6 hours to 21 months), found diffuse axonal injury in 12.6 per cent and diffuse hypoxic damage in 5.3 per cent. Although secondary brain-stem lesions were said to be "frequent", these authors stated that no patient with a

secondary lesion in the brain stem lived longer than four weeks.

The aim of this thesis, therefore, is to resolve these various discrepancies in our understanding of the structural basis of severe neurological disturbance in patients of prolonged survival after head injury. A comprehensive neuropathological analysis, with particular reference to diffuse axonal injury, secondary lesions in the brain stem and hypoxic brain damage, was carried out in a retrospective series of patients with a poor neurological outcome and who survived at least four weeks after a non-missile head injury.

CHAPTER 2

MATERIALS AND METHODS

Objectives of research

The main objectives of this study were as follows:-

1. To make a comprehensive survey of lesions present in the brains of patients who achieved a poor outcome (as defined below) after non-missile head injury.
2. In particular, to find the frequency of diffuse damage to white matter (henceforth called diffuse axonal injury), hypoxic brain damage and secondary brain-stem lesions.
3. Hence to identify the pathological basis for, or the lesion contributing most to, the neurological outcome of each patient studied.
4. To identify any complications of late onset which could account for deterioration in neurological state.

Design of study

It was decided to carry out a retrospective study of 48 cases identified from the files of the University Department of Neuropathology in the Institute of Neurological Sciences, Glasgow. This Department has a longstanding interest in the neuropathology of non-missile head injury and retains material from a total of 998 cases from 1961 to 1984 (inclusive). Selection of cases was primarily on clinical grounds, the only other requirement being a full neuropathological examination. The clinical criteria and neuropathological techniques are

described in the following sections. A total of 54 cases met the clinical criteria, but 6 of these were excluded since a histological examination had not been carried out. The remaining 48 cases represent 5 per cent of all fatal head injury cases in the Departmental records.

Clinical criteria for case selection

The clinical criteria for selection of cases were as follows:-

1. Head injury of "non-missile" type

   A non-missile head injury is essentially a blunt injury, although the term is intended to include penetrating wounds other than those caused by missiles. Causes of injury are given in the chapter on clinical data (p.15-17).

2. Survival of 28 days or more

   The study was restricted to patients alive at least 28 days after injury since this was considered to be the minimum survival at which the outcome according to the Glasgow Outcome Scale could be determined with reasonable accuracy (Jennett and Bond, 1975; Jennett et al., 1977a).

3. A poor neurological outcome

   The outcome was deemed to be poor if a patient had been incapable of independent life (i.e. Severely disabled or worse on the Glasgow Outcome Scale). For all cases, a detailed clinical summary had been included in the original post-mortem report. The majority of case records, however, were still available. In addition, patients treated in the Department of Neurosurgery of the Institute of Neurological

Sciences, Glasgow, from 1968 onwards had been subject to regular follow-up as part of a clinical study of the prognosis in severe head injury (Jennett et al. 1981). The data from these three sources (post-mortem reports, case records and clinical study) were collated and an assessment made of the outcome prior to death or terminal illness. Any cases of difficulty were referred for arbitration to Professor G.M. Teasdale, Professor of Neurosurgery in the University Department of Neurosurgery, Institute of Neurological Sciences, Glasgow.

Fuller clinical details of the outcomes of the patients are given in the chapter on clinical data (p.21-22). It should be emphasised at this stage, however, that patients who were "brain-dead" (Medical Royal Colleges, 1976) were excluded from the study.

4. Outcome due to brain damage whether primary or secondary relative to the moment of impact

Cases of disability due to spinal cord injury were excluded. Patients were also excluded if their neurological state was primarily due to extracranial complications, e.g. pneumonia or septicaemia.

Neuropathological examination

Gross examination

Brains and spinal cords were fixed for three weeks in 10 per cent formol saline prior to dissection in a standard manner, as follows. After transection of the midbrain, the cerebral

hemispheres were cut in serial coronal sections 1 cm thick. The cerebellum was dissected from the brain stem, bisected in the mid-sagittal plane and each hemisphere serially sectioned in 1 cm thick slices perpendicular to the folia. The brain stem was serially sectioned perpendicular to its long axis. Photographs of the gross specimens were available in 44 cases.

Histology

Large representative blocks of the cerebral and cerebellar hemispheres were embedded in celloidin and 30 μm sections stained by Nissl's method with cresyl violet and Woelcke's modification of Heidenhain's technique for myelin. In some cases, brain-stem blocks were also embedded in celloidin. Celloidin sections were scanned initially with a Watson Zoom stereo-microscope with transmitted light at magnifications of x10 to x50.

Blocks from standard sites in the cerebral hemispheres, representative of the main arterial territories, arterial boundary zones and basal ganglia, and also blocks of brain stem, were embedded in paraffin wax and stained with haematoxylin and eosin, a combined luxol fast blue/cresyl violet technique and Palmgren's method for axons.

Frozen sections of the brain stem and, in a few cases, the cerebral hemispheres also, were stained by the Marchi technique.

Quantitative methods

Quantitative methods were used to assess the severity of

contusions and the degree of hydrocephalus. The methods are explained in the appropriate chapters of the thesis.

Collection of data

All macroscopic and microscopic observations were charted on a series of line diagrams of the cerebral and cerebellar hemispheres, basal ganglia and brain stem. Clinical and pathological data were recorded on a proforma. The data were stored in the mainframe computer of the University of Glasgow.

Statistical analysis

Non-parametric methods were used for statistical analysis. Significance testing was by the χ^2 method, Fisher's exact test or the Mann-Whitney test.

CHAPTER 3

CLINICAL DATA

In this chapter various data relating to the 48 patients, their injuries, clinical course and management, and outcome, are summarised.

The Patients

Age

The median age of the patients when they were injured was 39.5 years (mean 38.8 years) with a range of 1-72 years (inter-quartile range 24.5-55.5 years).

Sex

There were 39 males (81% of the series) and 9 females (19%).

The Injury

Cause of injury

The causes of injury are given in Table 3.1. The majority were road traffic accidents, which accounted for 27 cases (56% of series), almost equally divided between vehicle occupants and pedestrians. Falls were the cause of injury in 13 cases (27%) and details of these are provided in Table 3.2. A total of 8 patients fell "from a height" ranging from a stationary lorry to several hundred feet, while 5 fell short distances, of adult height or less, e.g. falls to the ground while under the influence of alcohol. Assaults were the cause of injury in 8 cases (17%).

Table 3.1

Causes of injury.

				n	(%)
RTA*	Vehicle Occupant	Car	10		
		Motor cycle	2		
		Pedal cycle	1		
	Pedestrian		14		
	Total RTA			27	(56%)
Falls[1]	From height		8		
	Other		5		
	Total falls			13	(27%)
Assaults				8	(17%)
Total				48	(100%)

*RTA = Road traffic accident.

1 See Table 3.2

Table 3.2

Details of falls.

	Case No.	Description
From height	8	About 16 ft from ladder
	17	Down stairs
	19	From stationary lorry
	24	About 50 ft, from building
	26	Several hundred feet, while climbing
	27	Down lift shaft
	35	Down stairs
	46	Into ship's hold
Other falls	6	To ground
	15	Fainted during interview
	18	While boarding bus
	23	Infant - from high chair
	45	To ground

Extracranial injuries

Extracranial injuries were common in this series. Skeletal injuries were defined as "major" if they included fracture of a long bone, the pelvis or the vertebral column, and "minor" if there was a fracture of any other bone or dislocation of a joint. Soft-tissue or visceral injuries were similarly graded, as "major" if associated with haemo- or pneumo-thorax or haemo-peritoneum, and "minor" if these complications were not present.

Extracranial injuries were major in 17 patients (35% of series). These were skeletal only in 11 cases, a combination of skeletal and visceral in 5 cases and visceral only in 1 case. Major injuries were caused by road traffic accidents in 14 cases and falls "from a height" in 3 cases. Extracranial injuries were minor in 23 cases (48%). No extracranial injuries had been recorded in 8 cases (17%).

Clinical Course and Management

Lucid interval

A lucid interval after a head injury is a period of consciousness before subsequent lapse into coma. Reilly et al. (1975) defined a lucid interval as the ability to speak a short time after the injury. A lucid interval was described as "complete" when the patient is able to talk normally, but only "partial" when speech is abnormal (ranging from confused speech to a few muttered words only). In a series of fatal cases of head injury, these authors drew attention to the association between a lucid interval and secondary forms of brain damage,

including intracranial haematomas, hypoxic/ischaemic damage, meningitis and fat embolism. On the other hand, as Adams et al. (1977) pointed out, patients with severe primary brain damage are in coma from the outset without any lucid interval.

In the present series, a lucid interval occurred in only 9 patients (19%). This was complete in 4 cases (8%) and partial in 5 cases (11%).

Coma

Apart from any lucid interval, all the patients in the series were comatose, according to the Glasgow Coma Scale, for varying periods before any "recovery" to a vegetative or severely disabled state. There were 6 patients in the series, however, who remained in coma until they died.

Intracranial infection

Intracranial infection had been treated in 3 cases (6% of series). There was meningitis in 2 cases and a subdural empyema in 1 case.

Hypotension and hypoxia

Hypotension was defined arbitrarily as a systolic blood pressure < 90 mm Hg regardless of duration. Per-operative or anaesthetic induced hypotension was not taken into account since anaesthesia tends to protect against cerebral hypoxic damage. Hypoxia was defined arbitrarily as a $pO_2 \leqslant 60$ mm Hg regardless of duration. The data in this section refer to the month after injury, but

"terminal" hypotension, hypoxia and cardiac or respiratory arrests occurring in the 24 hours before death were disregarded.

Hypotension and/or hypoxia had been recorded in 26 cases (54% of series). Of this total, 9 were hypotensive only, including the single patient in whom a cardiac arrest occurred; 5 were both hypotensive and hypoxic; and 12 were hypoxic only, including 2 patients assumed to have been hypoxic in the absence of biochemical confirmation, since they had respiratory arrests necessitating temporary ventilation.

Neurosurgical procedures

A definitive neurosurgical procedure (i.e. excluding explorations and burrholes for intracranial pressure monitoring) was undertaken in 23 cases (48% of series). Details of these are given in Table 3.3.

Table 3.3

Neurosurgical procedures.

	Alone	Plus lobectomy	Plus bony decompression	Plus both	Total
Evacuation of haematoma	6	7	5	3	21
Debridement of contusions	-	1	-	-	1
Elevation of depressed fracture	1	-	-	-	1
Total	7	8	5	3	23

An intracranial haematoma (any type) was evacuated in 21 cases (44% of series). There were other procedures in 2 cases (4%). The operation included a lobectomy and/or bony decompression in 16 cases, in 15 of whom a haematoma had been evacuated.

Outcome

The 48 patients selected were incapable of independent life. It was possible to classify 44 of the patients more precisely as being in prolonged coma, in a vegetative state or severely disabled.

These distinctions were based on the ability to open eyes, to obey commands or to speak, the features used to determine conscious level on the Glasgow Coma Scale. Thus, the essential difference between prolonged coma and the vegetative state is that the latter is associated with eye opening (Jennett and Teasdale, 1977). If, on the other hand, a dependent patient was able either to speak or to obey commands, this was regarded as a degree of response inconsistent with a vegetative state and indicating severe disability as defined on the Glasgow Outcome Scale (p.3).

The different outcome categories are defined below:

1. Prolonged Coma (6 cases)

   Prolonged coma was defined as "not opening eyes, not obeying commands and not uttering words", of at least 28 days' duration.

2. Vegetative State (22 cases)

   The vegetative state was defined as "opening eyes, not obeying commands and not uttering words".

3. Severe Disability (16 cases)

   Severe disability was defined as "opening eyes, obeying commands or uttering words" in a patient unable to lead an independent life. One patient who was able to communicate by means of eye movements only and who may have been an example of the "locked-in" syndrome (Plum and Posner, 1980) was included in this group. This patient is described in more detail in Chapter 9.

4. Poor Outcome (Unspecified) (4 cases)

   Accurate classification was not possible in 4 cases. Clinical records relating to the period of recovery were no longer available in 3 cases. The fourth patient, a one year old infant, was too young for assessment by criteria intended for application to older patients.

Notwithstanding the above classification, the severity of outcome in the series as a whole is demonstrated by the fact that only 2 patients, both severely disabled, ever recovered sufficiently to be able to leave hospital.

Severely disabled patients who deteriorated

Three severely disabled patients deteriorated after an initial period of recovery, although they still remained within the Severe Disability group. These patients are described in more detail in Chapter 10.

Duration of survival

The duration of survival of the patients is tabulated with reference to outcome in Table 3.4. More than half of the series, 28 patients (58%), died within 90 days, while 39 patients (81%) died within one year of injury. The longest survival was of 14 years and 3 months, in a severely disabled patient.

Table 3.4

Duration of survival of patients (related to outcome).

	⩽90days	⩽180days	⩽1yr	⩽5yrs	⩽10yrs	⩽15yrs	Total
Prolonged coma	6	-	-	-	-	-	6
Vegetative state	13	2	2	3	2	-	22
Severe disability	7	5	1	1	1	1	16
Poor outcome (unspec.)	2	-	1	1	-	-	4
Total	28	7	4	5	3	1	48

CHAPTER 4

PRELIMINARY REMARKS ON PATHOLOGICAL FINDINGS

One of the principal purposes of this investigation was to identify the structural abnormalities of the brain that contribute to a poor outcome after non-missile head injury. Non-parenchymal lesions such as fractures of the skull and extradural haematomas were also studied, however, so that the survey would be sufficiently comprehensive to allow the analysis of relationships between different types of lesion and the delineation of patterns of brain damage.

Brain damage resulting from non-missile head injury is often classified as primary (i.e. occurring at the moment of injury) or secondary (i.e. developing later). This reflects not only temporal relationships but also pathogenesis since lesions caused directly by trauma are primary in that they are produced at the moment of injury. In clinical practice, the concept of secondary lesions is important because it draws attention to the occurrence of complications which may be preventable (Lancet, 1978). Recently, however, there has been a tendency for clinicians to classify lesions as focal or diffuse, with the aid of modern imaging techniques such as computerised tomographic scanning. This classification appears to be more relevant to outcome than the former, since a review of the literature has suggested that the lesions associated with a poor outcome are diffuse rather than focal in nature, with the exception of focal lesions in the brain stem.

In this thesis, the pathological findings are organised according to the scheme shown in Table 4.1. This classification takes into account whether lesions are primary or secondary as well as whether they are focal or diffuse. It should be noted that haematomas are here regarded as being primary since they are initiated at the moment of impact, although clinically they are thought of as secondary because they may not present until some time after injury, classically after a lucid interval. Diffuse axonal injury is also regarded as a primary lesion. This has been disputed by those who believed it to be secondary to complications of head injury (Osetowska, 1964; Jellinger, 1977) but diffuse axonal injury has since been reproduced in an experimental animal model and shown to occur at the moment of impact (Gennarelli et al., 1982).

Table 4.1

Classification of lesions used in this thesis.

Primary	Focal	Fractures of the skull Contusions Haematomas	Chapter 5
	Diffuse	Diffuse axonal injury	Chapter 6
Secondary	Focal	Evidence of raised intracranial pressure Secondary lesions in the brain stem	Chapter 7
	Focal or diffuse	Hypoxic/ischaemic brain damage Intracranial infection	Chapter 8
Delayed Onset		Hydrocephalus Causes of late deterioration	Chapter 10

CHAPTER 5

FOCAL PRIMARY LESIONS: FRACTURES OF THE SKULL, CEREBRAL CONTUSIONS AND INTRACRANIAL HAEMATOMAS

Fractures of the skull

Data on fractures of the skull have been augmented from clinical records, since fractures which had been recognised clinically were not always identifiable post mortem, particularly in patients of longer survival. There had been clinical evidence of a fracture in 26 patients (54% of series). Post mortem confirmation was obtained in 14 of these, representing all 8 patients who survived up to 38 days, but only 6 of 18 patients living longer. The clinical evidence of a fracture in the remaining 12 patients was radiographic in 8 cases, neurosurgical in 2 cases and based on the presence of cerebrospinal fluid rhinorrhoea or otorrhoea in 2 cases.

Fractures involved the vault of the skull alone in 7 cases (15% of series), the vault together with the base in 15 cases (31%) and the base alone in 4 cases (8%).

Cerebral contusions

The distribution and morphology of cerebral contusions is characteristic whether they are recent haemorrhagic lesions or longstanding shrunken pigmented scars. Typically they occur at the frontal and temporal poles and on the undersurfaces of the frontal and temporal lobes. When small they tend to affect the

crests of gyri but, if more severe, extend through the cortex and into the underlying white matter.

Quantification of contusions

The severity of contusions in each case was assessed by the "contusion index" method. Details of this technique have been published (Adams et al., 1985b), but a brief description will be given here.

Contusions within each of 12 anatomical "locators" (corresponding to the frontal, temporal, parietal, occipital lobes, the Sylvian fissures and the cerebellar hemispheres) are analysed separately. For each locator, the depth and extent of the contusions are each graded numerically as shown in Table 5.1. A "contusion index" (C.I.) is then derived for each locator by multiplying the figures for depth and extent. An example is given in Figure 5.1. The "total contusion index" (T.C.I.) for the whole brain is obtained by adding all the contusion indices, so that the T.C.I. has a potential range of 0-144.

Table 5.1

Contusion index method: gradings used for depth and extent of contusional damage.

Grade	Depth	Extent
0	Absent	Absent
1	Less than full thickness of cortex	"Localised", i.e. one gyrus or two adjacent gyri
2	Full thickness of cortex	"Moderately extensive" i.e. greater part of one surface of lobe
3	Into digitate white matter	"Extensive", i.e. more than one surface of a lobe
4	Into deep white matter	-

Contusions in the present series

There were no contusions (T.C.I. = 0) in 5 cases (10% of series). In the 43 cases (90%) in which contusions were present, they varied widely in severity (T.C.I. range 1-48, median 13). For simplicity, contusional damage was graded arbitrarily as absent (T.C.I. = 0) in 5 cases, mild (T.C.I. = 1-5) in 13 cases, moderate (T.C.I. = 6-24) in 22 cases and severe (T.C.I. = 25-48) in 8 cases. Of the 13 cases classified as mild, the contusions in 12 cases were small and localised and had a maximum extent of 1 in any locator.

The frequency and severity of contusions is compared for each locator and for each grade in Tables 5.2 and 5.3. Overall, contusions were most common and most severe in the temporal and frontal lobes, a pattern repeated within each grade. The most

marked difference between the mild and severe grades was the several-fold increase in both frontal and temporal contusion indices.

Table 5.2

Frequency of contusions (unilateral or bilateral) compared for each locator and each grade of severity. The figures in the final column are less than the totals in each row because in most cases there were contusions in more than one locator.

Grade	Locator*						
	F	T	SF	P	O	C	Any
Mild	6	6	2	0	3	4	13
Moderate	18	20	5	1	5	10	22
Severe	8	8	3	2	4	5	8
Total	32	34	10	3	12	19	43

Table 5.3

Median contusion indices (based on bilateral totals for each locator) compared for each locator and each severity grade.

Grade	Locator*					
	F	T	SF	P	O	C
Mild	1.5	2	2	0	1	1.5
Moderate	6	8	4	2	3	1
Severe	14.5	11.5	3	3	5	2
All cases	6.5	8	3.5	2	2	2

*F = frontal; T = temporal; SF = sylvian fissure; P = parietal; O = occipital; C = cerebellum

Relationship between contusions and fractures of the skull

Contusions were more severe in patients with a fracture of the skull than in those without a fracture (Table 5.4).

Table 5.4

Median total contusion indices (T.C.I.) in patients with and without a fracture of the skull.

	n	Median T.C.I.
With a fracture	26	16.5
Without a fracture	22	3.5

$p < 0.0001$ (Mann-Whitney test)

Intracranial haematomas

Intracranial haematomas were classified by anatomical type (Table 5.5) and according to whether or not evacuated neurosurgically. Most of the terms listed in Table 5.5 are in conventional use and are self-explanatory. A burst lobe is defined as an intra-cerebral haematoma in continuity with a subdural haematoma. With regard to intracerebral haematomas, a distinction has been made between intracerebral haematomas of the conventional type which are superficially located in the cerebral hemispheres, and basal ganglia haematomas which are deeply situated in the region of the basal ganglia (Adams et al., 1986b).

Table 5.5

Classification of haematomas used in this thesis.

Extradural		(EDH)
Intradural	Subdural	(SDH)
	Subarachnoid	(SAH)
	Burst lobe	(BL)
	Intracerebral	(ICH)
	Basal ganglia	(BGH)

Information on evacuation of haematomas was obtained from clinical records. The criterion of evacuation is intended to identify those haematomas which had been regarded as being clinically significant, but this is also a pragmatic approach to the problem of estimating size in a retrospective series, based on the assumption that haematomas which warranted neurosurgical intervention were in general larger than those not evacuated.

Intracranial haematomas in this series (Table 5.6)

Haematomas were present in 26 cases (54% of series). These had been evacuated in 21 cases (44%). In 5 cases (10%) there was post mortem identification of haematomas which had not been evacuated previously. Details of the haematomas in each group follow.

Evacuated haematomas (Table 5.6)

These were extradural and/or subdural in 7 cases, intracerebral in 2 cases (see Fig. 5.2) and a burst lobe in 9 cases. There was a combination of an extradural or subdural haematoma and a burst lobe or intracerebral haematoma in 3 cases.

Table 5.6

Evacuated and unevacuated haematomas according to type.

Type*	Evacuated	Unevacuated	Total
EDH	1	-	1
SDH	5	2	7
EDH + SDH	1	-	1
SAH	-	1	1
BL	9	-	9
ICH	2	2	4
BGH	-	-	-
SDH + ICH	1	-	1
EDH + BL	2	-	2
Total	21	5	26

*Abbreviations as in Table 5.5 (p.31).

Evacuated haematomas thus involved cerebral parenchyma (as intracerebral haematomas or burst lobes) in 14 cases. The anatomical locations of these are shown in Table 5.7.

Table 5.7

Location of evacuated intracerebral haematomas and burst lobes.

Location*	Unilateral	Bilateral	Total
F	4	-	4
T	9	1	10
P, O, C	-	-	-
Total	13	1	14

*Abbreviations as in Tables 5.2 and 5.3 (p.29).

The temporal lobe was the most common site, accounting for 10 of the 14 cases, including 1 case with bilateral evacuated temporal haematomas (Fig. 5.1).

Unevacuated haematomas (Table 5.6)

In 5 cases the haematomas had not been evacuated previously. These were small, with none of the intracerebral haematomas, for example, being greater than 2 cm in diameter. There were no examples of basal ganglia haematomas in the series.

Relationship between intracranial haematomas and fractures of the skull (Table 5.8)

There was a statistically significant association between intracranial haematomas (any type) and fractures of the skull. The relationship between evacuated haematomas and fractures of the skull was also statistically significant.

Table 5.8

Relationship between haematomas and fractures of the skull.

	Fracture		Total	p*
	Present (n=26)	Absent (n=22)		
Haematoma (any type)	18	8	26	0.02
Evacuated haematoma	15	6	21	0.03

*Fisher's exact probability test

Relationship between intracranial haematomas and cerebral contusions (Table 5.9)

Cerebral contusions were more severe in patients with an intracranial haematoma of any type than in patients without an intracranial haematoma.

Table 5.9

Cerebral contusions in patients with and without an intracranial haematoma (any type).

		n	Median TCI*
Haematoma (any type)	Present	26	16.5
	Absent	22	4.0

p = 0.0002 (Mann-Whitney test)

*TCI = Total contusion index.

Interrelationships between primary focal lesions

Interrelationships between fractures of the skull, cerebral contusions and intracranial haematomas in 43 cases are summarised in Fig. 5.3. There was a combination of contusions with a fracture of the skull and/or an intracranial haematoma in 36 cases. Contusions were present without a fracture or a haematoma in 7 cases. In no case did a fracture or a haematoma constitute the only focal primary lesion.

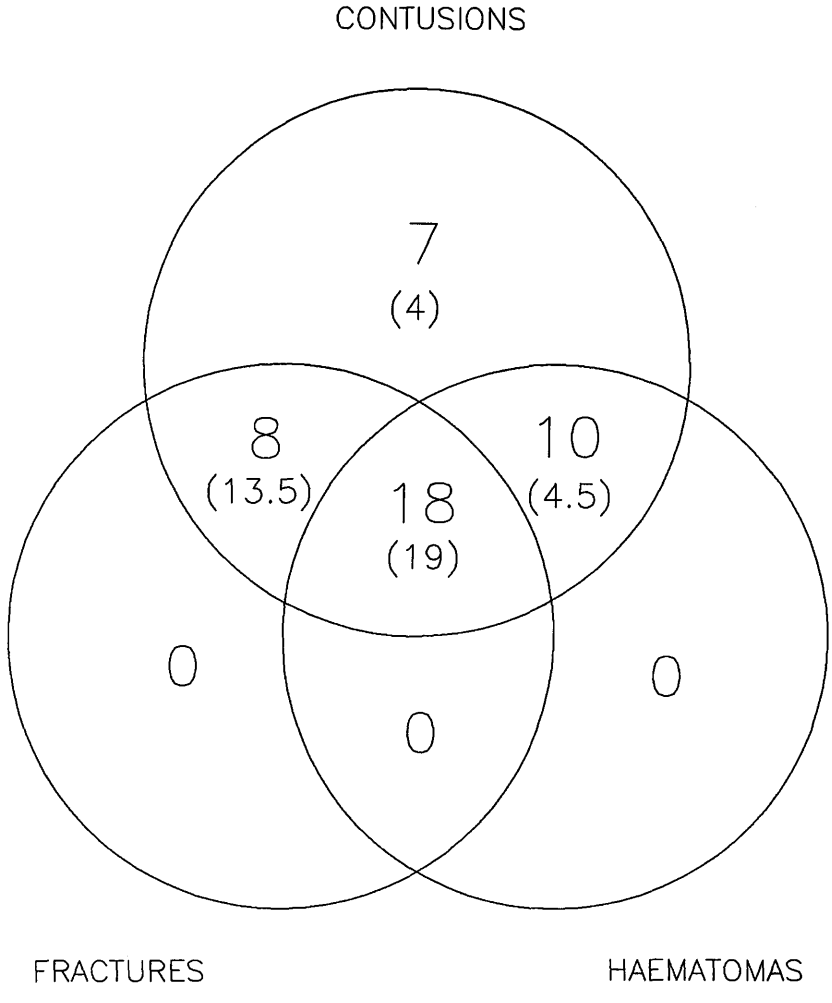


Fig. 5.3

Venn diagram showing inter-relationships between cerebral contusions, intracranial haematomas (any type) and fractures of the skull in 43 cases. Median total contusion indices within each compartment are given in parentheses.

CHAPTER 6

DIFFUSE PRIMARY BRAIN DAMAGE: DIFFUSE AXONAL INJURY

Introduction

Primary damage to white matter is characterised by evidence of widespread damage to axons in the cerebral hemispheres, the cerebellum and brain stem. This process has been known by various names, including diffuse degeneration of cerebral white matter (Strich, 1956), shear injury of the brain (Peerless and Rewcastle, 1967), diffuse damage of immediate impact type (Adams et al., 1977) and diffuse axonal injury (Adams et al., 1982). The last term, diffuse axonal injury, is the one preferred in this thesis since it clearly denotes that axons are the seat of the fundamental lesion.

The histological features of diffuse axonal injury depend on the length of survival. Thus, Strich (1961) found that in patients of up to six weeks' survival, evidence of axonal injury took the form of retraction balls similar to those described by Cajal (1928) after section of peripheral nerves, and that in patients living longer, extensive Wallerian degeneration was demonstrable up to two years after injury by means of the Marchi method. In patients surviving beyond the period of active myelin degeneration, demyelination is the main feature (Osetowska, 1964; Bethlem, 1968). The time course of the principal histological features may therefore be summarised as follows: retraction balls (days to weeks); Wallerian degeneration (months); and, demyelination (years).

In cases of diffuse axonal injury, small focal lesions are commonly found in the corpus callosum and dorsolateral quadrants of the rostral brain stem (Strich, 1961). These lesions, which are often visible macroscopically, tend to be haemorrhagic when recent but, if the patient survives for some time, they become pigmented shrunken or cystic scars. They have been called the hallmarks of diffuse axonal injury (Adams et al., 1980a), forming part of a diagnostic triad comprising (i) a focal lesion in the corpus callosum, (ii) a focal lesion in one or both dorsolateral quadrants of the rostral brain stem, and (iii) microscopic evidence of diffuse damage to axons (Adams et al., 1982; Adams and Graham, 1984). More recently, however, the same authors have drawn attention to examples of diffuse axonal injury without the characteristic focal lesions, which they have designated as "microscopic diffuse axonal injury" (Adams et al., 1985a).

Diffuse axonal injury in this series

In the present series, not all cases of diffuse axonal injury were accompanied by focal lesions of the type described above. For the purposes of this thesis, therefore, diffuse axonal injury was defined simply as "widespread evidence of axonal damage indicated by retraction balls, Wallerian degeneration or demyelination, and which could not be attributed to any proximal focal lesion(s)".

According to this definition, diffuse axonal injury was present in 25 cases in the series (52% of total). Retraction

balls (Fig. 6.1) were present in 12 cases (survival 28-64 days). Wallerian degeneration as demonstrated by the Marchi technique (Fig. 6.3) was found in 12 cases (survival 59 days to 1 year 9 months). In many of these cases, abundant lipid phagocytes were visible within areas of myelin degeneration in conventionally stained sections (Fig. 6.2). Demyelination as recognised by pallor of myelin staining (Fig. 6.4) was present in 10 cases (survival 140 days to 14 years 3 months), and in one of these (survival 6 years) was so severe that it was obvious to the naked eye (Fig. 6.5). Thus the main histological features of diffuse axonal injury to some extent overlapped chronologically.

Focal lesions in the corpus callosum and brain stem.

Focal lesions in the corpus callosum (Figs. 6.6 and 6.12) or the dorsolateral quadrant of the rostral brain stem (Figs. 6.7 and 6.8) were present in 24 of the 25 cases of diffuse axonal injury. The relationship between lesions in each situation, and whether these were macroscopic or microscopic, is shown in Table 6.1. Focal lesions were present in the corpus callosum in 24 cases, and in the dorsolateral quadrant of the rostral brain stem in 18 cases. In only 18 of the 25 cases of diffuse axonal injury was the original diagnostic triad of Adams et al. (1982) fulfilled, in that there were lesions in both the corpus callosum and the dorsolateral quadrant of the rostral brain stem. Both lesions were visible macroscopically in only 13 cases (Table 6.1).

Table 6.1

Focal lesions in the corpus callosum and dorsolateral quadrant of the rostral brain stem in 25 cases of diffuse axonal injury. Macroscopic and microscopic lesions are distinguished.

		Focal lesion in corpus callosum			
		Macro*	Micro*	Absent	Total
Focal lesion in dorsolateral quadrant	Macro*	13	-	-	13
	Micro*	4	1	-	5
	Absent	4	2	1	7
	Total	21	3	1	25

* Macro = macroscopic; Micro = microscopic

Grading of diffuse axonal injury according to focal lesions in the corpus callosum and brain stem

Diffuse axonal injury has been reproduced in an experimental animal model by Gennarelli et al. (1982). These authors were able to correlate the duration of traumatic coma in primates with the severity of diffuse axonal injury as graded according to the presence or absence of focal lesions in the corpus callosum or the dorsolateral quadrant of the rostral brain stem. Grade 3 diffuse axonal injury (the most severe) was characterised by focal lesions in both the corpus callosum and the dorsolateral quadrant of the rostral brain stem, together with histological evidence of diffuse damage to axons. Grade 2 was characterised by a focal lesion in the corpus callosum only,

together with histological evidence of diffuse damage to axons. Grade 1 (the least severe) was characterised by histological evidence of diffuse damage to axons without accompanying focal lesions. In the present series, diffuse axonal injury could be classified similarly (Table 6.2). Thus, diffuse axonal injury was of Grade 3 in 18 cases, Grade 2 in 6 cases and Grade 1 in 1 case. These gradings will be related to outcome in Chapter 9.

Table 6.2

Grading of diffuse axonal injury in 25 cases.

Grade of diffuse axonal injury	Microscopic diffuse axonal damage	Focal lesions		n
		Corpus callosum	Dorsolateral quadrant of rostral brain stem	
3	+	+	+	18
2	+	+	-	6
1	+	-	-	1

Other Features Associated with Diffuse Axonal Injury

Microglial clusters

Groups of hypertrophied microglial cells, variously known as microglial "stars", "knots" or "clusters", occur scattered throughout white matter in cases of diffuse axonal injury (Strich, 1961; Mitchell and Adams, 1973; Adams et al., 1977). They are difficult to appreciate in conventional paraffin

sections but are easily recognised in celloidin sections stained by Nissl's method (Figs. 6.9 and 6.10). In the present study, 20μ thick paraffin sections stained with cresyl violet were also examined for this purpose. Microglial clusters were present in 40 cases who survived up to 1 year 174 days. They were a constant finding in cases of diffuse axonal injury, being found in all 21 cases within the stated period of survival. They were also, however, found in 19 cases without diffuse axonal injury. Assessment was subjective, but in general the numbers and distribution of microglial clusters differed between cases with and without diffuse axonal injury. In cases with diffuse axonal injury, microglial clusters were very numerous and widespread. They tended to be superficial rather than deep, medial rather than lateral, superior rather than inferior, and therefore were often most numerous in parasagittal white matter although asymmetry between the hemispheres was common. In cases without diffuse axonal injury, on the other hand, clusters tended to be too scanty to conform to the pattern described and appeared to be scattered randomly.

Multiple small lesions of haemorrhagic or ischaemic origin: "diffuse vascular injury"

Small haemorrhages and softenings, small cortical infarcts situated at the bottom of sulci, and sclerosis of Ammon's horns were observed by Strich (1956) in her cases of diffuse degeneration of white matter. Similar small or microscopic lesions were found in this series, but were not always

associated with diffuse axonal injury. Since the lesions tended to be widely scattered in the brain and appeared to have originated as foci of haemorrhage or ischaemic damage often related to small vessels, it seemed appropriate to consider them in this section under the title of "diffuse vascular injury". A difficulty in this area is the lack of a precise descriptive term for the individual lesions since their pathogenesis is speculative and histologically they range from minute infarcts, haemorrhagic infarcts, haemorrhages and minute haematomas to older foci of gliosis often with evidence of previous haemorrhage. The lesions in the depths of sulci have been called "sulcal infarcts", while those in the dorsal paramedian regions of the cerebral hemispheres are conventionally known as "gliding contusions", although there is little resemblance between these and conventional infarcts or contusions. In this study, however, the terms sulcal infarct and gliding contusion will be retained, while the term "vascular lesion" will be used, in spite of its limitations, for similar lesions elsewhere in the brain. Various possible components of diffuse vascular injury were separated according to their location in the cerebral hemispheres (Table 6.3). These will be described in turn and their relationship to diffuse axonal injury analysed.

Table 6.3

Components of diffuse vascular injury.

Sulcal infarcts

Gliding contusions

Vascular lesions in:

- hippocampi
- white matter
- basal ganglia
- subependymal zone

Sulcal infarcts. The term sulcal infarct is intended to denote a lesion of ischaemic or haemorrhagic origin occurring within the cerebral cortex immediately underlying the deepest part of the sulcus (Figs. 6.5, 6.12 and 6.13). Sulcal infarcts were present in 13 cases (27% of series). There was a highly significant association with diffuse axonal injury (Table 6.4). In some cases they were visible to the naked eye as small pigmented foci of cortical atrophy at the bottom of sulci (Figs. 6.5, 6.12). Microscopically (Fig. 6.13) they consist of small foci of subtotal or total neuronal loss with reactive gliosis and evidence of previous haemorrhage in the form of haemosiderin either free or within macrophages, although this last feature was not always present. The full thickness of the cortex could be involved, but frequently the lesion was confined to the deeper layers only. Characteristically, sulcal infarcts were most prominent and most frequent in the superior and middle

frontal sulci, which were involved in 12 of the 13 cases, and diminished in size and frequency the farther lateral the affected sulci. Asymmetry was common, with contralateral lesions often absent or occurring at a different level.

Table 6.4

Relationship between different components of diffuse vascular injury and diffuse axonal injury.

Type of lesion	n	Diffuse axonal injury		p*
		Present (n=25)	Absent (n=23)	
Sulcal infarcts	13	13	0	<0.0001
Gliding contusions	18	16	2	<0.0001
Vascular lesions in:				
Hippocampi	22	21	1	<0.0001
White matter	17	15	2	0.0002
Basal ganglia	22	15	7	0.04
Subependymal zone	16	11	5	0.09
Any type	36	24	12	0.0005
>1 type	24	20	4	<0.0001

*Fisher's exact probability test

Gliding contusions. The term gliding contusion was introduced by Lindenberg and Freytag (1960) to refer to haemorrhages and haematomas at the dorsal paramedian portions of the cerebral hemispheres. Gliding contusions are frequently seen in patients

with diffuse axonal injury (Adams and Graham, 1984; Adams et al., 1986b).

In the present series, gliding contusions (Figs. 6.6 and 6.12) were found in 18 cases (38% of series). There was a significant association between gliding contusions and diffuse axonal injury (Table 6.4). In some cases the contusions were visible macroscopically as pigmented streaks in the parasagittal white matter (Figs. 6.6, 6.12). More commonly, they could only be detected microscopically as zones of intense gliosis associated with haemosiderin deposition (Fig. 6.14), often extending into the deeper layers of the cortex at the supramedial angle as a zone of neuronal loss and gliosis.

Vascular lesions in the hippocampi. Focal lesions of an ischaemic or haemorrhagic nature (Fig. 6.11) were found in one or both hippocampi in 36 cases (75% of series). After exclusion of 14 cases in which there was hypoxic brain damage of diffuse or boundary zone type, or infarction in the territory supplied by the posterior cerebral artery, there remained 22 cases with what may be regarded as "isolated" vascular lesions in the hippocampi. There was a highly significant association between these isolated lesions and diffuse axonal injury (Table 6.4). Histologically, neuronal loss and reactive gliosis were seen in the Sommer sector with or without concomitant involvement of the endfolium. In 10 of the 22 cases there was evidence of previous haemorrhage in the form of haemosiderin lying free or within macrophages. This haemorrhagic type of lesion tended to occur

in a characteristic location, at the junction of the Sommer sector and the subiculum rather than in the Sommer sector itself.

Vascular lesions in white matter. Multiple minute haemorrhagic lesions or, in patients of longer survival, microscopic foci of gliosis with haemosiderin deposition (Fig. 6.15), as distinct from gliding contusions, were found in the white matter in 17 cases (35% of series). There was a highly significant association with diffuse axonal injury (Table 6.4). They tended to occur in deep rather than superficial white matter and were often related to small vessels. The anatomical distribution is shown in Table 6.5: the frontal and temporal lobes were most frequently involved.

Table 6.5

Location of multiple vascular lesions in the white matter in 17 cases.

	n
Frontal lobe	11
Temporal lobe	16
Parietal lobe	0
Occipital lobe	4
Cerebellum	1

Vascular lesions in the region of the basal ganglia. The region of the basal ganglia was defined as the area including the

corpus striatum, the caudate and lentiform nuclei, the internal capsule and also the thalamus, hypothalamus and subthalamic region. Multiple foci of gliosis or minute infarcts with haemosiderin deposition, with associated neuronal loss when in grey matter, were present in 22 cases (46%) (Fig. 6.12). These were associated with diffuse axonal injury (Table 6.4).

Vascular lesions in subependymal zone Foci of gliosis with haemosiderin deposition occurring in a subependymal situation in the walls of the lateral or third ventricles were present in 16 cases (33% of series). These were not significantly associated with diffuse axonal injury.

Relationship between diffuse axonal injury and diffuse vascular injury

Any evidence of vascular injury of the types described above was strongly associated with diffuse axonal injury (Table 6.4). This was particularly the case when more than one type of vascular lesion was present (Table 6.4).

Relationship between diffuse axonal injury and focal primary brain damage

Fractures of the skull and intracranial haematomas were more frequent in patients without diffuse axonal injury than in patients with diffuse axonal injury (Table 6.6). Cerebral contusions were more severe in patients without diffuse axonal injury than in patients with diffuse axonal injury (Table 6.7).

Table 6.6

Relationship between diffuse axonal injury, fractures of the skull and intracranial haematomas.

	n	Diffuse Axonal Injury		p*
		Present (n=25)	Absent (n=23)	
Fractures of skull	26	10	16	0.038
Haematomas (any type)	26	9	17	0.008
Haematomas (evacuated)	21	5	16	0.0006

*Fisher's exact probability test

Table 6.7

Cerebral contusions in patients with and without diffuse axonal injury.

	Diffuse Axonal Injury	
	Present	Absent
Median TCI*	4	17
n	25	23

p = 0.0036 (Mann-Whitney test)

*TCI = Total contusion index.

CHAPTER 7

SECONDARY BRAIN DAMAGE: RAISED INTRACRANIAL PRESSURE AND SECONDARY LESIONS IN THE BRAIN STEM

Raised intracranial pressure

Expanding intracranial space-occupying lesions will ultimately lead to a high intracranial pressure. This has important complications, notably infarction within particular arterial territories and haemorrhage or infarction in the brain stem. These secondary effects are mediated by shift and internal herniation of the brain (Lindenberg, 1955). Tentorial ("uncal" or "lateral transtentorial") herniation can be inferred post mortem from grooving in the parahippocampal gyrus, often associated with "pressure" necrosis (Lindenberg, 1955), marking the impression of the free edge of the tentorial membrane. Similar necrosis of herniated tissue also occurs in supra-callosal ("subfalcine") and in tonsillar herniation. Adams and Graham (1976) investigated the relationship between ventricular fluid pressure and different manifestations of internal herniation. Pressure necrosis in the parahippocampal gyrus was found in 30 of 34 cases shown to have a high ventricular fluid pressure ($\geqslant$ 20 mm Hg) on continuous pressure monitoring, and was the feature most often associated with a high pressure. Pressure necrosis due to tentorial herniation is thus good evidence that intracranial pressure has been high during life, and in the present study will provide a means of verifying the pathogenesis of lesions considered to be secondary in type, particularly secondary lesions in the brain stem and (in the

next chapter) infarction in the territories of particular arteries.

Pressure necrosis in the parahippocampal gyrus in the present series

Pressure necrosis is represented by a linear zone of necrosis or, in patients of longer survival, scarring which is superficially located in the cortex of the medial aspect of the parahippocampal gyrus (Figs. 7.1 and 7.2), and tends to be wedge-shaped in histological sections (Fig. 7.4). The lesion may not always be visible to the naked eye. In the present series, pressure necrosis in one or both parahippocampal gyri was identified in 28 cases (58% of total). The lesion was seen macroscopically in 16 cases and only microscopically in the remaining 12 cases.

Primary factors in cases with pressure necrosis

Of the 28 cases with pressure necrosis in the parahippocampal gyrus, an intracranial haematoma had been present in 17 cases. In 16 of these cases the haematoma had been evacuated. The relationship between pressure necrosis and haematomas in general was not statistically significant. Pressure necrosis was, however, more frequent in cases in which a haematoma had been evacuated than in cases without evacuation of a haematoma (Table 7.1). Diffuse axonal injury was present in 11 of the 28 cases, although in 3 of these there had also been evacuation of a haematoma. Pressure necrosis was more frequent in the absence

of diffuse axonal injury than in cases with diffuse axonal injury (Table 7.1). Contusions were more severe in cases with pressure necrosis (Table 7.2) than in cases without pressure necrosis.

Table 7.1

Relationships between pressure necrosis in the parahippocampal gyrus (PHG), haematomas and diffuse axonal injury.

	Pressure necrosis in PHG		n	p*
	Present (n=28)	Absent (n=20)		
Haematomas (any type)	17	9	26	0.22
Haematomas (evacuated)	16	5	21	0.03
Diffuse axonal injury	11	14	25	0.03

* Fisher's Exact Probability Test.

Table 7.2

Cerebral contusions in cases with and without pressure necrosis in the parahippocampal gyrus (PHG).

	Pressure necrosis in PHG	
	Present	Absent
Median TCI*	14	4
n	28	20

p = 0.02 (Mann-Whitney test)

*TCI = Total contusion index

Secondary lesions in the brain stem

The distinction between primary and secondary focal lesions in the brain stem

Previous studies on damage to the brain stem resulting from head injury have tended to concentrate on focal lesions and have neglected diffuse axonal injury (e.g. Jellinger, 1983). Even when a distinction has been made between primary and secondary focal lesions, the relationship of the former to diffuse axonal injury has not always been appreciated (e.g. Rosenblum et al., 1981). Mitchell and Adams (1973), however, established that focal lesions of primary type are a feature associated with diffuse axonal injury. These authors reasoned that if evidence of an elevated intracranial pressure was absent, then any structural abnormalities in the brain stem must be considered to be primary. In a series of fatal non-missile head injuries without pressure necrosis in the parahippocampal gyrus, the only focal lesions identified in the brain stem occurred in the region or one or both superior cerebellar peduncles and these were invariably associated with diffuse axonal injury.

On the other hand, evidence of raised pressure does not necessarily mean that a lesion in the brain stem is secondary, since pressure necrosis is common in cases of diffuse axonal injury (Adams et al., 1982; this study, Table 7.1). Tomlinson (1970) reviewed patterns of brain stem damage in relation to pathogenesis. Apart from multiple small haemorrhages associated with instantaneous death or very short survival, Tomlinson recognised "primary delayed" and "secondary" types. Primary

delayed damage was characterised by the features of diffuse axonal injury, together with areas of ischaemic necrosis (with or without associated haemorrhage) which tended to occur in the tissues bordering the lateral mesencephalic sulcus, the superior cerebellar peduncles or the colliculi. Smaller, usually microscopic, lesions also occurred more centrally in the upper pons, midbrain or diencephalon. In contrast, the haemorrhages, haemorrhagic infarcts or infarcts which constitute secondary lesions are typically centred on the midline in the upper pons although often spreading laterally, particularly within the tegmentum of the pons and midbrain. An exception to this is so-called Kernohan notch or "Kernohan-Woltman crescent" (Kernohan and Woltman, 1929), which is an area of ischaemic necrosis on the lateral aspect of the cerebral peduncle contralateral to a supratentorial space-occupying lesion. Tomlinson admitted the possibility that herniation could produce laterally-placed lesions which might simulate primary lesions, although he considered that these must be uncommon except for the Kernohan notch. More recently, Jellinger (1983) has pointed out that primary and secondary lesions may not always be distinguished on morphological grounds.

Thus, while neither evidence of an elevated intracranial pressure nor morphological characteristics may be trustworthy in determining whether a lesion is primary or secondary, the presence or absence of diffuse axonal injury would appear to be a major factor in the interpretation of focal lesions in the brain stem. Mitchell and Adams (1973) went as far as to suggest

that primary damage localised to the brain stem does not exist, although this view may have been tempered in the light of at least one type of focal lesion known to occur in the absence of diffuse axonal injury: the traumatic ponto-medullary "tear" or "avulsion", attributed to hyperextension of the head, is usually rapidly fatal (Lindenberg and Freytag, 1970; Leestma, Kalelkar and Teas, 1983) although rare survivals of up to 26 days have now been recorded (Pilz, Strohecker and Grobovschek, 1982; Pilz, 1983a).

In the present study focal lesions in the brain stem were classified as primary or secondary by taking into account their relationship with diffuse axonal injury and their morphological characteristics. Thus, focal lesions in cases with diffuse axonal injury were regarded as being primary (provided that they were located in one or both dorsolateral quadrants), and focal lesions in cases without diffuse axonal injury (apart from any examples of the ponto-medullary tear) were assumed to be secondary in origin. These assumptions will be tested by analysing and comparing the relationship of primary and secondary lesions to evidence of a raised intracranial pressure.

Focal brain-stem lesions in the present series

Diffuse axonal injury was present in 25 cases in the series. In 17 of these, there were focal lesions in the brain stem, all situated in the dorsolateral quadrant(s) in the region of the superior cerebellar peduncles. These were regarded as primary lesions consistent with the diagnosis of diffuse axonal injury.

Focal brain-stem lesions associated with diffuse axonal injury have been analysed in Chapter 6 (p.37).

Diffuse axonal injury was not present in the remaining 23 cases. In 14 of these there were focal lesions in the brain stem. The pattern, extent and distribution of these are summarised in Table 7.3. The cases could be classified into two main groups according to whether the main lesions were visible macroscopically (8 cases) or microscopically only (6 cases). The macroscopic lesions ranged in type from a haematoma (in one case only - Fig. 7.5) to cystic or shrunken infarcts (Figs. 7.3 and 7.6). The macroscopic lesions in particular were more or less extensive lesions involving different parts of the brain stem but including the tegmentum of the midbrain and or pons in 7 of the 8 cases. In the remaining case (no. 37) the macroscopic lesion, a Kernohan notch, was confined to the cerebral peduncle although there was also a separate microscopic lesion in the basis pontis. Kernohan notches (Fig. 7.6) were present in a total of three cases.

Table 7.3 Patterns of brain stem damage and areas of brain stem involved in 14 cases with secondary lesions in the brain stem.

Pattern of Damage		Case No.	Areas of brain stem involved			
			Tegmentum		Cerebral peduncle	Basis pontis
			Midbrain	Pons		
Macroscopic lesions present	Median infarct	8	M*	M	-	-
		18	M	M	-	M
	Median infarct plus separate paramedian lesions	30	M	-	-	M
		42	M	-	-	-
		15	M	M	-	M
	Median infarct plus Kernohan notch	6	M	M	M	M
		5	M	M	M	M
		37	-	-	M	m
Microscopic lesions only	Minute infarcts or foci of gliosis	4	m*	-	-	-
		14	-	-	m	-
		19	-	-	m	-
		25	-	m	-	-
		28	m	-	-	-
		33	m	-	-	m

*M = macroscopic; m = microscopic

Relationship between focal lesions in the brain stem and evidence of a high intracranial pressure

Cases with and without diffuse axonal injury have been tabulated separately with respect to focal lesions in the brain stem and evidence of a high intracranial pressure in the form of pressure necrosis in the parahippocampal gyrus (Tables 7.4 and 7.5). Overall, there was no relationship between focal lesions of primary type and pressure necrosis. On the other hand, pressure necrosis was present in all cases with secondary lesions in the brain stem, and the relationship between pressure necrosis and secondary lesions in the brain stem was statistically highly significant.

Table 7.4

Relationship between primary focal lesions in the brain stem and pressure necrosis in the parahippocampal gyrus (PHG) in 25 cases with diffuse axonal injury.

		Pressure Necrosis (PHG)		
		Present	Absent	Total
Focal brain-stem lesion (primary)	Present	8	10	18
	Absent	3	4	7
	Total	11	14	25

p = 0.65 (Fisher's Exact Probability Test)

Table 7.5

Relationship between secondary focal lesions in the brain stem and pressure necrosis in the parahippocampal gyrus (PHG) in 23 cases without diffuse axonal injury

		Pressure Necrosis (PHG)		
		Present	Absent	Total
Focal brain-stem lesion (secondary)	Present	14	0	14
	Absent	3	6	9
	Total	17	6	23

$p = 0.0008$ (Fisher's Exact Probability Test)

CHAPTER 8

SECONDARY BRAIN DAMAGE: HYPOXIC AND ISCHAEMIC BRAIN DAMAGE; INTRACRANIAL INFECTION

Hypoxic and ischaemic brain damage

Brain damage due to hypoxia or ischaemia was common, being present in 27 cases (56% of series). The lesions are analysed below according to pathogenetic type (diffuse hypoxic brain damage; ischaemic damage in arterial boundary zones; infarction within arterial territories; and, infarction in the region of the basal ganglia). The results are summarised in Table 8.1. The relationship between a high intracranial pressure and the different types of hypoxic and ischaemic damage will be examined.

Diffuse hypoxic brain damage (Table 8.1)

There was diffuse hypoxic brain damage in 2 cases (4% of series). In one of these (case 23), neuronal loss was almost total in the occipital lobes but more anteriorly tended to be restricted to sulci. There was patchy neuronal loss in the corpus striatum. Hypoxic damage in the cerebellum was confined to the boundary zones between the territories supplied by the superior and posterior inferior cerebellar arteries.

In the other (case 42 - Fig. 8.1), damage was more severe. Neuronal loss was virtually total in the occipital lobes. More anteriorly, neuronal loss had a laminar distribution (Fig. 8.2) but was asymmetrical and in the right cerebral hemisphere tended

Table 8.1 Types and distribution of hypoxic or ischaemic brain damage in 27 cases (abbreviations overleaf).

CASE	DIFFUSE			BOUNDARY ZONE			ARTERIAL TERRITORY				REGION OF BASAL GANGLIA				
	CH	Cb	BG	A/MCA	M/PCA	S/PICA	ACA	MCA	PCA	SCA	GP	IC	Th	HTh	Other
23	+	+	+												
42	+	+	+						R		L	L			
4		+	+	B	R								R		
21				B	R	L									
24			+	B	B										
25			+	L			B	L	L		B	B	R		SN(B) P(L)
30			+	B		L									
5							B	L	L		B	B		L	SN(B) RN(L)
6									B		L			L	OT(L)
18									B		R	L	R	R	MB(B) SN(L)
33									L		B	B	L		LGB(L)
37									B		B	R	L	L	
40									R	B		R			CN(R) P(R)
7										L					
8									B	R					
9								R							
13										R					
14								L							
28									R						
31								L	L						
41									L	B					
46										B					
3												L			CN(L) P(L)
15											L	B	B		SN(R)
16													R	R	
17											B				
32											L				AN(L)

Table 8.1 (cont.) Abbreviations used in table

AN	Amygdaloid nucleus
ACA	Anterior cerebral artery
A/MCA	Boundary zone between territories of ACA and MCA
AT	Arterial territory
B	Bilateral
BG	Basal ganglia (including diencephelon)
CN	Caudate nucleus
Cb	Cerebellum
CH	Cerebral hemispheres
GP	Globus pallidus
HTh	Hypothalamus
IC	Internal capsule
L	Left
LGB	Lateral geniculate body
MB	Mamillary bodies
MCA	Middle cerebral artery
M/PCA	Boundary zone between territories of MCA and PCA
OT	Optic tract
P	Putamen
PICA	Posterior inferior cerebellar artery
R	Right
SCA	Superior cerebellar artery
SN	Substantia nigra
S/PICA	Boundary zone between territories of SCA and PICA
Th	Thalamus

to be confined to sulci. There was total neuronal loss in the thalamus. In the cerebellum neuronal loss was patchy on the left side and total on the right side (Fig. 8.1). In this case there was also microscopic evidence of previous tentorial herniation, with infarction in the territory of the posterior cerebral artery on the right side (Fig. 8.1) and small infarcts in the tegmentum of the midbrain.

Ischaemic brain damage in arterial boundary zones (Table 8.1)

Ischaemic damage was present in boundary zones between arterial territories in 5 cases (10% of series) (Fig. 8.3). The boundary zone between the territories of the anterior and middle cerebral

arteries was involved in all 5 cases (bilateral in 4). There was concomitant involvement of other boundary zones (between the territories of the middle and posterior cerebral arteries, or the superior and posterior inferior cerebellar arteries) in 4 cases. The lesions took the form of infarction in 3 cases and multifocal neuronal loss in 2 cases. An interesting finding was the presence of subtotal diffuse neuronal loss in the thalamus in 4 of the 5 cases.

Infarction within arterial territories (Table 8.1)

Infarction within the territories of the principal arteries supplying the cerebral hemispheres or cerebellum (anterior, middle and posterior cerebral arteries; superior and posterior inferior cerebellar arteries) was present in 17 cases (35% of series). There was involvement of a single territory only in 7 cases and more than one territory in 10 cases. The arteries concerned were: the posterior cerebral artery in 12 cases (Figs. 7.2 and 8.1); the superior cerebellar artery in 6 cases; the middle cerebral artery in 5 cases (Fig. 8.4) and the anterior cerebral artery in 2 cases. There were no cases with infarction involving the territory of the posterior inferior cerebellar artery.

Apart from differences in territories involved, there were wide variations between cases in the extent of infarction, ranging from small infarcts confined to a single sulcus, or multiple small infarcts, to large lesions comprising entire arterial territories.

Infarction in the region of the basal ganglia (Table 8.1)

Infarcts situated deeply within the cerebral hemispheres, involving the basal ganglia, internal capsules or diencephalon, were present in 14 cases (29% of series). Only lesions which were visible macroscopically have been included in this total. Small haemorrhagic lesions forming part of a more generalised diffuse vascular injury of the type associated with diffuse axonal injury (p. 40) have been excluded.

There was infarction involving the globus pallidus in 10 cases (bilateral in 5) (Fig. 7.2a), the thalamus in 7 cases (bilateral in 1) (Fig. 7.2b) and the hypothalamus in 5 cases (all unilateral) (Fig. 7.2a). Infarcts involved the internal capsule in 9 cases (bilateral in 4) (Figs. 8.5 and 9.2). In two cases with diffuse axonal injury (Nos. 3 and 40), there was what appeared to have been unilateral haemorrhagic infarction involving the head of the caudate nucleus, the internal capsule and the putamen (Fig. 6.11). There was diffuse axonal injury in both cases and it is possible that these "capsular" infarcts are another manifestation of vascular damage associated with diffuse axonal injury. Other sites less frequently involved by infarction are included in Table 8.1.

Relationship between hypoxic and ischaemic brain damage and a high intracranial pressure (Table 8.2)

In the majority of cases with hypoxic or ischaemic brain damage, there had been a high intracranial pressure according to the criterion of pressure necrosis in one or both parahippocampal

gyri. The association with pressure necrosis was statistically significant for infarction in the territory of the posterior cerebral artery, and for infarction involving the globus pallidus, the thalamus and the internal capsule. When any type of hypoxic or ischaemic brain damage, or any arterial territory infarct, or any infarct in the region of the basal ganglia was present, there was a strong association with pressure necrosis.

Table 8.2

Relationship between different types of hypoxic/ischaemic brain damage and pressure necrosis in the parahippocampal gyrus (PHG). Abbreviations as in Table 8.1 (p.60).

Type of Hypoxic/ Ischaemic damage	Pressure necrosis in PHG		n	p*
	Present (28 cases)	Absent (20 cases)		
Arterial Territory				
ACA	2	0	2	0.3
MCA	4	1	5	0.3
PCA	12	0	12	0.0004
SCA	5	1	6	0.2
Any AT	15	2	17	0.002
"Basal Ganglia"				
GP	9	1	10	0.02
Th	7	0	7	0.02
HTh	4	1	5	0.3
IC	9	0	9	0.004
Any site	13	1	14	0.002
Boundary Zone	4	1	5	0.3
Diffuse	1	1	2	0.8
Any Type	22	5	27	0.0003

*Fisher's Exact Probability Test

Intracranial infection

There was clinical or pathological evidence of intracranial infection in four patients. In two of these acute purulent meningitis had been recognised and treated. At autopsy there appeared to have been complete resolution without any residual meningitis or meningeal thickening. In the third case (No. 10) an extradural/subdural empyema had formed after a craniotomy for evacuation of a burst temporal lobe. The empyema was drained but the patient subsequently developed hydrocephalus which was treated with a ventriculo-peritoneal shunt. When the patient died 54 days after his injury, dissection of the brain showed a small abscess within the left temporal lobe which extended up to the wall of the temporal horn of the lateral ventricle (Fig. 5.1). Histologically, there was a subacute ventriculitis. In the fourth case (No. 32), post-mortem examination 140 days after injury revealed a small abscess in the left frontal lobe (Fig. 8.6) without any clinical history of intracranial infection. A craniotomy had been performed for evacuation of a burst left temporal lobe.

CHAPTER 9

CLINICO-PATHOLOGICAL CORRELATION

The principal lesions and the clinical outcomes in every case are listed in Table 9.1. As identified in the foregoing survey, there was contusional damage in 43 cases, hypoxic or ischaemic damage in 27 cases, diffuse axonal injury in 25 cases, and secondary lesions in the brain stem in 14 cases. The number of cases with each of these lesions in each outcome group is shown in Table 9.2. Contusions were present in all or nearly all the cases in each outcome group, but the other lesions varied more in frequency. Thus, excluding cases with a poor outcome (unspecified), diffuse axonal injury was present in 15 of 22 cases (68%) in a vegetative state, but in only 2 of 6 cases (33%) of prolonged coma; hypoxic or ischaemic damage ranged in frequency from 4 of 6 cases (67%) of prolonged coma, to 11 of 22 cases (50%) in a vegetative state; and secondary lesions in the brain stem were found in 4 of 6 cases (67%) of prolonged coma, but in only 5 of 22 cases (23%) in a vegetative state.

The distribution of the different outcomes found in association with diffuse axonal injury, cerebral contusions or hypoxic/ischaemic damage broadly reflected the distribution of these outcomes in the series as a whole, but a relatively high proportion of cases with a secondary lesion in the brain stem were in prolonged coma (Table 9.2).

Table 9.1 Principal lesions and clinical outcome in all 48 cases (Abbreviations overleaf).

Case No.	DAI (Grade)	Contusions (Severity)	H.I.B.D. (Type)	S.B.S.L. (Extent)	Outcome
1	3	Mod			PO(U)
2	3	Sev			PC
3	3	Mild	BG		VS
4		Mod	BZ + BG	m	PC
5		Mod	AT + BG	M	PC
6		Mod	AT + BG	M	PC
7	2	Mod	AT		SD
8		Mod	AT	M	PC
9	3	Mild	AT		VS
10	3	Mod			PC
11	2	Mild			SD
12	3				VS
13	3	Mild	AT		VS
14		Sev	AT	m	SD
15		Sev	BG	M	VS
16		Sev	BG		SD
17			BG		SD
18		Mod	AT + BG	M	VS
19		Mod		m	SD
20	3	Mild			VS
21		Mild	BZ		SD
22	3	Mod			VS
23			Diff		PO(U)
24		Mod	BZ		VS
25		Mod	BZ+AT+BG	m	VS
26	3				VS
27	3	Mild			VS
28		Sev	AT	m	SD
29	1	Mod			VS
30		Mod	BZ	M	VS
31		Mod	AT		SD
32	2	Sev	BG		SD
33		Mild	AT+BG	m	SD
34	2	Mod			SD
35	2	Mod			VS
36	3				SD
37		Mod	AT+BG	M	PO(U)
38	3	Mild			VS
39		Sev			VS
40	3	Mild	AT+BG		PO(U)
41	3	Mod	AT		VS
42		Mod	Diff+AT+BG	M	VS
43		Mod			SD
44	3	Mild			VS
45		Sev			SD
46	3	Mod	AT		VS
47	2	Mild			SD
48	3	Mild			VS
Totals	25	43	27	14	

Table 9.1 (continued). Abbreviations used in table.

AT	Infarction in arterial territory
BG	Infarction in region of basal ganglia (as defined on p.62)
BZ	Infarction in distribution of arterial boundary zone
DAI	Diffuse axonal injury
Diff	Diffuse hypoxic brain damage
HIBD	Hypoxic/ischaemic brain damage
m	Microscopic secondary lesion in the brain stem
M	Macroscopic secondary lesion in the brain stem
Mod	Moderate contusional damage
PC	Prolonged coma
PO(U)	Poor outcome (unspecified)
SBSL	Secondary lesion in the brain stem
SD	Severe disability
Sev	Severe contusional damage
VS	Vegetative state

Table 9.2

Occurrence of lesions according to clinical outcome. (Abbreviations as in Table 9.1).

Lesion	Outcome				
	V.S. (n=22)	P.C. (n=6)	S.D. (n=16)	P.O(U) (n=4)	n
D.A.I.	15	2	6	2	25
Contusions	20	6	14	3	43
H.I.B.D.	11	4	9	3	27
S.B.S.L.	5	4	4	1	14

The analysis in this section has simply dealt with types of lesion in isolation and has not taken into account either the combinations of lesions present in individual cases or differences in the severity of lesions. These factors are examined below.

Combinations of lesions

It is clear from Tables 9.1 and 9.2 that more than one type of lesion was present in the majority of cases. This is more easily appreciated when the data are expressed in the form of a Venn diagram (Fig. 9.1). More than one type of lesion was present in 40 cases (83% of series). Only in 8 cases was there a single type of lesion, whether as diffuse axonal injury (3 cases), or hypoxic/ischaemic damage (2 cases), or contusions (3 cases). There were no cases in which a secondary lesion in the brain stem was the only finding: other lesions were always present, specifically cerebral contusions and also, in every case but one, hypoxic or ischaemic damage.

Thus the Venn diagram (Fig. 9.1) emphasises the heterogeneity of the series and the multiplicity of the lesions in the majority of cases. Even when more than one type of lesion was present, however, they may not all have contributed equally or even significantly to the eventual outcome. The more detailed analysis below attempts to identify those lesions of particular importance.

The most important lesions

Diffuse axonal injury

Of the 25 cases with diffuse axonal injury, this was the only lesion present in 3 cases. In all of the other 22 cases, there were cerebral contusions, and in 8 of these there was also additional ischaemic damage. The contusions were graded as mild in 11 cases, moderate in 9 cases, and severe in 2 cases. The

hypoxic/ischaemic damage took the form of infarcts in all cases and these involved a major arterial territory in 5 cases, the region of the basal ganglia in 2 cases, and both a major arterial territory and the region of the basal ganglia in 1 case.

Thus the lesions accompanying diffuse axonal injury were essentially focal. Contusions when present were mild in half the cases. A priori it is likely that these other lesions were relatively unimportant in the context of diffuse axonal injury. If this assumption is correct, then the outcome in cases with diffuse axonal injury ought to be related to the grade of diffuse axonal injury (p. 38). The relationship between the outcome and the grade of diffuse axonal injury is shown in Table 9.3. There were 23 cases of diffuse axonal injury in which the

Table 9.3

Relationship between clinical outcome and grade of diffuse axonal injury (excluding cases of poor outcome (unspecified)).

Outcome	Grade of Diffuse Axonal Injury			Total
	1	2	3	
Vegetative State	1	1	13	15
Prolonged Coma	0	0	2	2
Severe Disability	0	5	1	6
Total	1	6	16	23

$\chi^2 = 14.03$ $\quad 0.01 > p > 0.001$

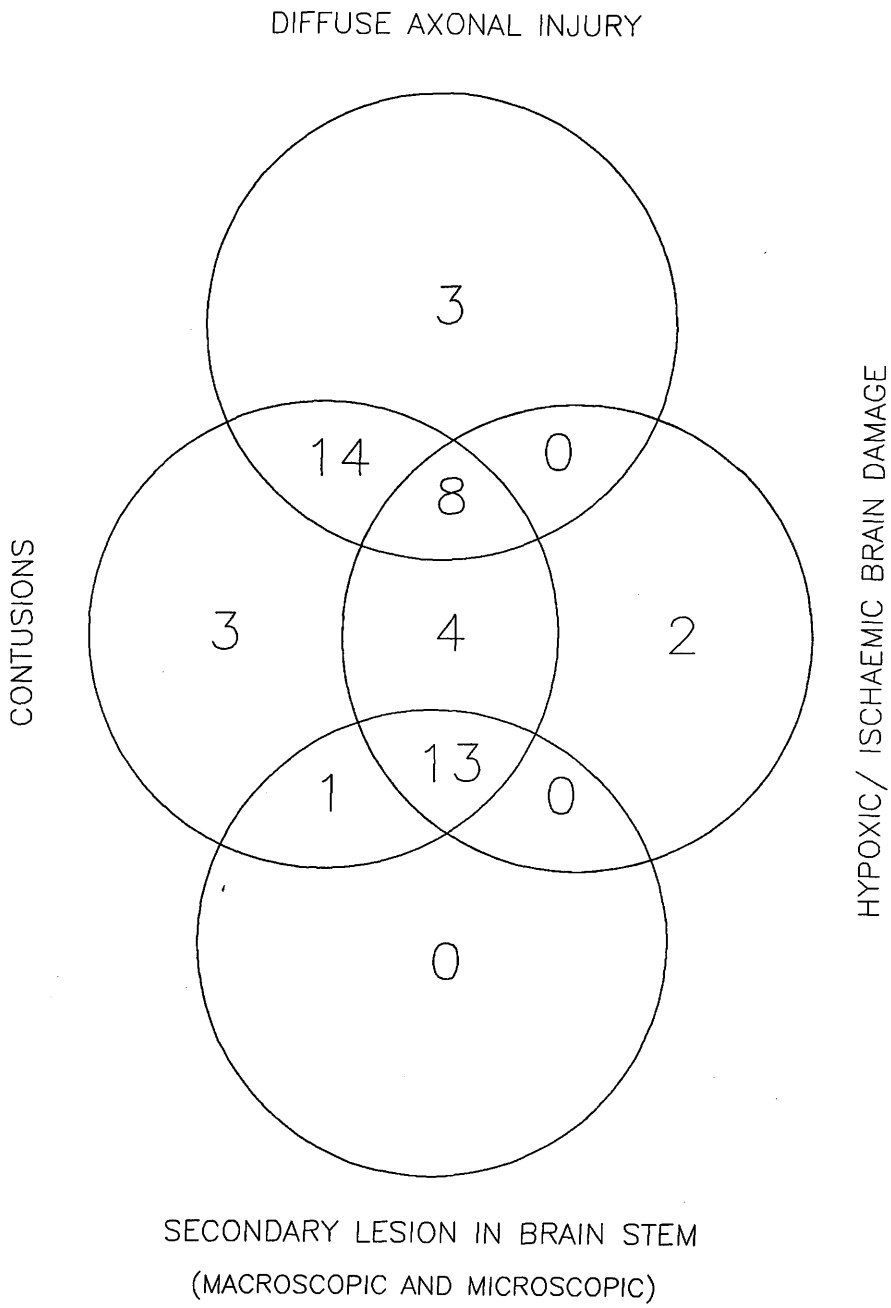


Fig. 9.1

Venn diagram showing inter-relationships between principal lesions in all 48 cases.

Table 9.4

Relationship between clinical outcome and extent of secondary brain-stem lesion, excluding cases with diffuse or boundary-zone hypoxic brain damage.

Outcome	Secondary Brain Stem Lesion		Total
	Microscopic	Macroscopic	
Vegetative State	0	2	2
Prolonged Coma	0	3	3
Severe Disability	4	0	4
Total	4	5	9

$$\chi^2 = 8.98 \qquad 0.02 > p > 0.01$$

in the brain stem. While they may have contributed to disability, they were trivial lesions which were probably relatively unimportant. There were no cases in which these were the only type of lesion or could have constituted the sole cause of severe disability.

Hypoxic or ischaemic brain damage

There were 27 cases with hypoxic or ischaemic brain damage. If 8 cases with diffuse axonal injury and 8 cases with a macroscopic secondary brain-stem lesion are excluded, then 11 cases remain. The outcome was known in 10 of these, and appeared to be related to the main type of hypoxic or ischaemic damage present (Table 9.5). Three of 4 cases with diffuse or boundary-zone hypoxic damage were in a vegetative state or prolonged coma, but all 6 patients with infarction involving arterial territories or the region of the basal ganglia were severely disabled.

Table 9.5

Relationship between outcome and main type of hypoxic/ischaemic brain damage, excluding cases with diffuse axonal injury or macroscopic secondary lesions in the brain stem. Abbreviations as in Table 9.1 (p.67).

Outcome	Main type of H.I.B.D.		Total
	Diff/BZ	AT/BG	
Vegetative state	2	0	2
Prolonged coma	1	0	1
Severe disability	1	6	7
Total	4	6	10

$\chi^2 = 6.5 \qquad 0.05 > p > 0.02$

Cerebral contusions

Thus far, the outcome in the majority of cases, or at least whether a patient was vegetative or comatose rather than severely disabled, would appear to have been determined by the grade of diffuse axonal injury, the type of hypoxic/ischaemic damage or the extent of a secondary lesion in the brain stem, suggesting that contusions were relatively unimportant. In Table 9.6, the median total contusion indices (TCI) are compared between each outcome group, in cases with diffuse axonal injury, cases with hypoxic/ischaemic damage or secondary brain-stem lesions, and cases with cerebral contusions only. In cases with diffuse axonal injury the median TCI in vegetative patients was only 4 as compared with 16.5 for severely disabled patients. For cases with hypoxic/ischaemic damage or secondary lesions in

Table 9.6

Comparison of median total contusion indices (range in parentheses) between each outcome group in cases with diffuse axonal injury, cases with hypoxic/ischaemic brain damage, and cases with contusions only. Abbreviations as in Table 9.1 (p.67).

	V	PC	SD
DAI	4 (3-14) n = 13	20.5 (15-26) n = 2	16.5 (1-35) n = 5
HIBD/SBSL	15.5 (7-30) n = 6	18.5 (12-24) n = 4	1 n = 1
Contusions only	48 n = 1	-	26.5 (21-32) n = 2

the brain stem, the median TCI was similar for all three outcome groups, suggesting that the severity of contusions did not account for the differences in outcome. There were 3 cases in which contusions were the only lesions identified. Two of these cases (median TCI = 26.5) were severely disabled, but the third case was vegetative with a TCI of 48, the highest equal TCI recorded in the series. The other case in the series with a TCI of 48 (in addition to infarcts in the region of the basal ganglia) was severely disabled. In general, the least severe contusions were found in vegetative patients with diffuse axonal injury.

Conclusions

Based on the Venn diagram in Fig. 9.1, and assuming that

contusions were relatively unimportant, five main lesions or combinations of lesions have been identified. These are: diffuse axonal injury (25 cases); hypoxic/ischaemic damage (6 cases); hypoxic/ischaemic damage together with a secondary lesion in the brain stem (13 cases); contusions with a secondary lesion in the brain stem (1 case); and, contusions alone (3 cases). The different outcomes have been broken down according to these categories in Table 9.7. Diffuse axonal injury emerges as the most frequent cause of the vegetative state (15 of 22 cases), and as a common cause of severe disability (6 of 16 cases). The combination of hypoxic/ischaemic damage and a secondary lesion in the brain stem was the most frequent finding in cases of prolonged coma (4 of 6 cases).

Table 9.7

Outcome related to most important pathological findings. Abbreviations as in Table 9.1 (p.67).

	V	PC	SD	PO(U)	Total
DAI	15	2	6	2	25
HIBD	1	0	4	1	6
HIBD + SBSL	5	4	3	1	13
Contusions + SBSL	0	0	1	0	1
Contusions	1	0	2	0	3
Total	22	6	16	4	48

Table 9.8

Outcome related to most important pathological findings, excluding microscopic secondary lesions in the brain stem. Abbreviations as in Table 9.1 (p.67).

	V	PC	SD	PO(U)	Total
DAI	15	2	6	2	25
HIBD	2	1	7	1	11
Macroscopic SBSL + HIBD	4	3	0	1	8
Contusions	1	0	3	0	4
Total	22	6	16	4	48

If it is assumed that microscopic secondary lesions in the brain stem were also relatively unimportant, then the number of categories can be reduced to four (Table 9.8): diffuse axonal injury (25 cases); hypoxic/ischaemic damage (11 cases); hypoxic/ischaemic damage together with a macroscopic secondary lesion in the brain stem (8 cases); and, contusions (4 cases). When microscopic secondary lesions in the brain stem are excluded, hypoxic/ischaemic damage becomes the most frequent finding in cases of severe disability (Table 9.7).

The lesions particularly associated with a vegetative state or prolonged coma were grade 3 diffuse axonal injury, diffuse or boundary-zone hypoxic brain damage, and a macroscopic secondary lesion in the brain stem. Together these accounted for 24 of the 28 cases in a vegetative state or prolonged coma.

Relationship between lucid interval and pathological findings

The relationship between a complete or partial lucid interval and the most important pathological findings is shown in Table 9.9. For simplicity, cases with hypoxic/ischaemic damage or a secondary lesion in the brain stem (macroscopic or microscopic) have been grouped together as having secondary lesions. None of the 25 cases with diffuse axonal injury, but 1 of 3 cases with contusions and 8 of 20 cases with a secondary lesion, experienced a lucid interval.

Table 9.9

Relationship between a lucid interval (complete or partial) and the most important pathological findings in each case.

Main lesion	Lucid Interval		Total
	Present	Absent	
Diffuse axonal injury	0	25	25
Contusions only	1	2	3
Secondary lesions*	8	12	20
Total	9	39	48

$$\chi^2 = 12.13 \quad 0.01 > p > 0.001$$

*Hypoxic/ischaemic brain damage or secondary lesion in the brain stem (macroscopic or microscopic).

Relationship between evacuation of an intracranial haematoma and pathological findings

The relationship between evacuation of an intracranial haematoma and the most important pathological findings is shown in Table

9.10. Again, cases with secondary lesions such as hypoxic/ischaemic damage and secondary brain-stem lesions have been grouped together. Evacuation of a haematoma had been most frequent in the cases in which a secondary lesion was the main lesion present, having been performed in 14 of the 20 cases (70%), and was almost as frequent in the cases with contusions (60%). Evacuation of a haematoma had been least common in the cases with diffuse axonal injury, having occurred in only 5 of the 25 cases (20%).

Table 9.10

Relationship between evacuation of an intracranial haematoma and the most important pathological findings in each case.

Main Lesion	Evacuation of a Haematoma		Total
	Yes	No	
Diffuse axonal injury	5	20	25
Contusions	2	1	3
Secondary lesion*	14	6	20
Total	21	27	48

$\chi^2 = 11.98$ $\quad 0.01 > p > 0.001$

*Hypoxic/ischaemic damage or secondary lesions in the brain stem (macroscopic or microscopic).

A possible case of post-traumatic locked-in syndrome

The term "locked-in syndrome" (Plum and Posner, 1980) refers to a clinical state in which patients are quadriplegic and mute but awake and able to communicate by eye movements. There is

preservation of hearing, comprehension and intelligence, but this may not be recognised clinically since there is complete immobility and apparent inability to communicate (Plum and Posner, 1980). Bricolo (1975) believed that the syndrome had not been observed after trauma, but the case below (No. 33 in this series) is described because of features suggestive of the locked-in syndrome. Although the pathological findings are not typical, the case is instructive because it illustrates the profound neurological disturbance which can result from strategically-placed small lesions, and also because it demonstrates the value of histology in the interpretation of post-traumatic brain damage.

Case history

This 17 year old boy was admitted to hospital after a blow on the head. He had not been unconscious. While under observation he became increasingly drowsy with severe headache and vomiting, then had a seizure and subsequently developed a right hemiparesis. The left pupil was fixed and dilated. After transfer to the Institute of Neurological Sciences, the patient was not opening his eyes or giving a verbal response and was extending his limbs to painful stimuli. Both pupils were now fixed and dilated. A computerised tomographic (CT) scan showed a left-sided extra-dural haematoma. This was evacuated through a craniotomy. Post-operatively the intracranial pressure remained high (30mm Hg), but a CT scan showed brain swelling only. By the time of discharge back to the referring hospital 9

days after injury, the patient was still not opening his eyes or giving a verbal response and was flexing his limbs to painful stimuli. He required to be tube fed. Spontaneous eye-opening returned but there was little further improvement although some 3 months after the injury it was noticed that he could blink answers to simple questions, e.g his age, and answer yes or no. There was no further improvement and a series of chest infections culminated in the patient's death some 5 months after injury.

Post-mortem examination

General. There was very little subcutaneous fat and there was generalised reduction in muscle bulk. The feet were plantar flexed and there were flexion contractures of wrists, elbows, knees and hips. There was normal growth of head and body hair. On internal examination, the only finding of note was a severe purulent bronchitis.

Neuropathology. The brain weighed 1400g. Grooves in both parahippocampal gyri delineated previous tentorial herniae. Coronal sections revealed a solitary small contusion in the left inferior frontal gyrus and confirmed the presence of pressure necrosis in both parahippocampal gyri. Apart from this, the main findings on gross examination were small infarcts in the cerebral hemispheres. These were present as follows:-

1. The medial segment of each globus pallidus
2. The substantia nigra on each side (Fig. 9.2a)

3. Extending from the left lateral geniculate body across the posterior limb of the internal capsule into the lateral nuclear complex of the left thalamus (Fig. 9.2b)
4. The medial part of the left pulvinar
5. The cortex on the undersurface of the left occipital lobe

The cerebral cortex was otherwise normal. The ventricles were symmetrical and of normal size. The interventricular septum was intact. Sections of the brain stem and spinal cord showed an abnormally white appearance in the medullary pyramids and the crossed pyramidal tracts.

Histology. Histological examination of paraffin and celloidin sections confirmed the presence of the infarcts seen grossly but also demonstrated infarcts at the lower ends of the internal capsules immediately proximal to the cerebral peduncles. There was no evidence of diffuse hypoxic damage affecting the cerebral cortex, basal nuclei, hippocampi or cerebellum. There was no evidence of diffuse axonal injury in paraffin or frozen sections. Sections of the brain stem revealed a microscopic infarct in the median raphe of the basis pontis, but in addition there was bilateral, symmetrical, long-tract degeneration of the cortico-spinal tracts in the brain stem and spinal cord (Fig. 9.3).

Comment

The pathological basis for the patient's neurological state was not clear on gross examination. Although small infarcts had been identified, these were not thought sufficient to account for the clinical findings or the extent of long-tract degeneration, and neither diffuse hypoxic damage nor diffuse axonal injury could be excluded. Histological examination, however, ruled out these possibilities, and showed that bilateral, symmetrical long-tract degeneration was secondary to small infarcts in the internal capsules whose extent had not been fully apparent previously. These and the other infarcts in this case could all be attributed to the effects of raised intracranial pressure and internal herniation secondary to an extradural haematoma.

The patient had clinically been regarded as vegetative and it was only in the light of the pathological findings that the case records were reviewed and the patient's apparent ability to communicate by eye movements discovered. This suggested a level of higher cortical function incompatible with the vegetative state and in keeping with the locked-in syndrome. For this reason the patient was classified as severely disabled for the purposes of this study. If this is an example of the locked-in syndrome, the pathological findings are not typical. Characteristically, there is a brain-stem infarct which interrupts the motor pathways but spares the reticular activating system and the cerebral hemispheres (Nordgren et al., 1971; Reznik, 1983). In the present case, although a minute

infarct was present in the median raphe of the basis pontis, the main lesions were small infarcts situated at the lower ends of the internal capsules.

CHAPTER 10

COMPLICATIONS OF DELAYED ONSET

Hydrocephalus

Hydrocephalus is a common finding in patients of long survival after severe head injury in both ante-mortem (Meyers et al., 1983) and post-mortem studies (Strich, 1961; Jellinger, 1977). Jellinger (1977) claimed that hydrocephalus (although not defined) was present in 50% of his cases of post-traumatic encephalopathy. In the present series also hydrocephalus appeared to be common, but in order to test this more objectively, and also allow correlation with other factors, quantification was attempted. The method is described below.

Quantification of hydrocephalus

The method entailed point-counting of photographs of coronal brain slices. For each case one photograph of a level including thalamus or hypothalamus was selected. This criterion was intended to introduce some uniformity but was met in only 37 of the 44 cases for which photographs were available. The photographs were then copied on to transparencies which were projected on to perforated peg-board. Using the perforations for point-counting, the number of "hits" scored by the whole brain slice (including the ventricles) and the ventricles respectively were recorded. If the lateral ventricles were unequally enlarged, counts were taken from the half of the slice

with the smaller ventricle and then doubled to give values for the whole coronal section. This was to minimise the effect of possibly unrepresentative compensatory hydrocephalus secondary to focal destructive lesions of the cerebral parenchyma. In this way, about 600 points were counted per case. The Ventricle-Brain Ratio (VBR) was then calculated from (ventricle score/ brain score) x 100. The standard error percentage of the method ranged from 0.4 to 2.0% depending on the size of the ventricles.

Results

Normal controls were not studied because of the difficulty of obtaining these. Instead a normal range for the VBR was defined arbitrarily, based on the original gross descriptions of the dissected brains. In cases described as having normal ventricles, the highest VBR was 5.0, while in those considered to have dilated ventricles the lowest VBR was 5.8. A VBR of 5.5 was therefore chosen as the upper limit of normal. VBR's for the 38 cases analysed are listed together with age, brain weight and length of survival in Table 10.1. In one case (No. 47) hydrocephalus was of late onset, secondary to a cerebellar haematoma of hypertensive origin. Excluding this case, ventricular dilatation was present in 24 of the 37 cases (65%).

The relationship between VBR and duration of survival was analysed (Table 10.2). Overall (Fig. 10.1) and also for subgroups characterised respectively by diffuse lesions (i.e. diffuse axonal injury and diffuse hypoxic brain damage) and by

Table 10.1

Age, survival, brain weight and ventricle/brain ratio (VBR) in 38 cases for which the VBR could be assessed.

Case No.	Age	Survival	Brain Wt.	VBR
2	60	29	1250	6.3
3	29	30	?	2.8
4	27	30	1160	5.8
6	61	34	1440	2.7
7	56	34	1450	3.9
9	36	38	1560	2.9
10	63	39	1350	9.0
11	17	41	1620	3.1
13	18	43	1490	3.4
14	61	47	1755	6.6
15	29	51	1490	7.3
16*	17	54	1420	6.5
17	40	56	?	2.7
18	38	57	1250	2.6
19	64	59	1360	8.1
20	59	59	1370	3.6
21	72	60	1270	5.0
22	47	64	1390	6.2
24	43	71	1350	7.0
25	24	73	1520	6.7
26	29	82	1650	3.3
27	15	86	1160	3.3
30	65	105	1440	11.3
32	55	140	?	14.6
33	17	147	1400	4.0
34	60	157	?	12.7
36	48	220	1230	6.9
37	48	252	1250	7.2
38	56	277	1190	7.2
39	31	462	1020	7.5
40	34	539	1070	12.8
41	18	640	1200	11.4
42	15	1087	1140	28.5
43	48	1161	1120	11.2
44	20	2195	1020	12.1
45	53	3023	?	10.7
46	42	3114	1220	18.0
47*	43	5206	1280	15.4

*Notes

Case 16 Ventriculoperitoneal shunt (clinical obstructive hydrocephalus)

Case 47 Terminal obstructive hydrocephalus (cerebellar haemorrhage)

focal lesions only, there was a positive correlation between VBR and duration of survival (Table 10.2). When clinical outcome was taken into account, correlation between VBR and survival was strongest for cases of diffuse axonal injury in a vegetative state or prolonged coma (Fig. 10.1). For other outcome groups, respectively with diffuse axonal injury and with focal lesions only, the correlation was less marked (Table 10.2).

Table 10.2

Correlation between duration of survival and ventricle/brain ratio.

	n	r	p
Series overall	37	.55	.001
Diffuse lesions*	20	.60	.01
Diffuse axonal injury	19	.68	.01
Diffuse axonal injury (vegetative/coma)	13	.88	.001
Diffuse axonal injury (severely disabled)	5	.57	NS
Focal lesions only	17	.54	.05
Focal lesions only (vegetative/coma)	8	.285	NS
Focal lesions only (severely disabled)	8	.71	.05

*Diffuse lesions = diffuse axonal injury or diffuse hypoxic brain damage.

Cause of hydrocephalus

Apart from the case of a cerebellar haematoma of late onset noted above, the greatest ventricular enlargement was associated with diffuse lesions. The highest VBR (28.5) occurred in a case

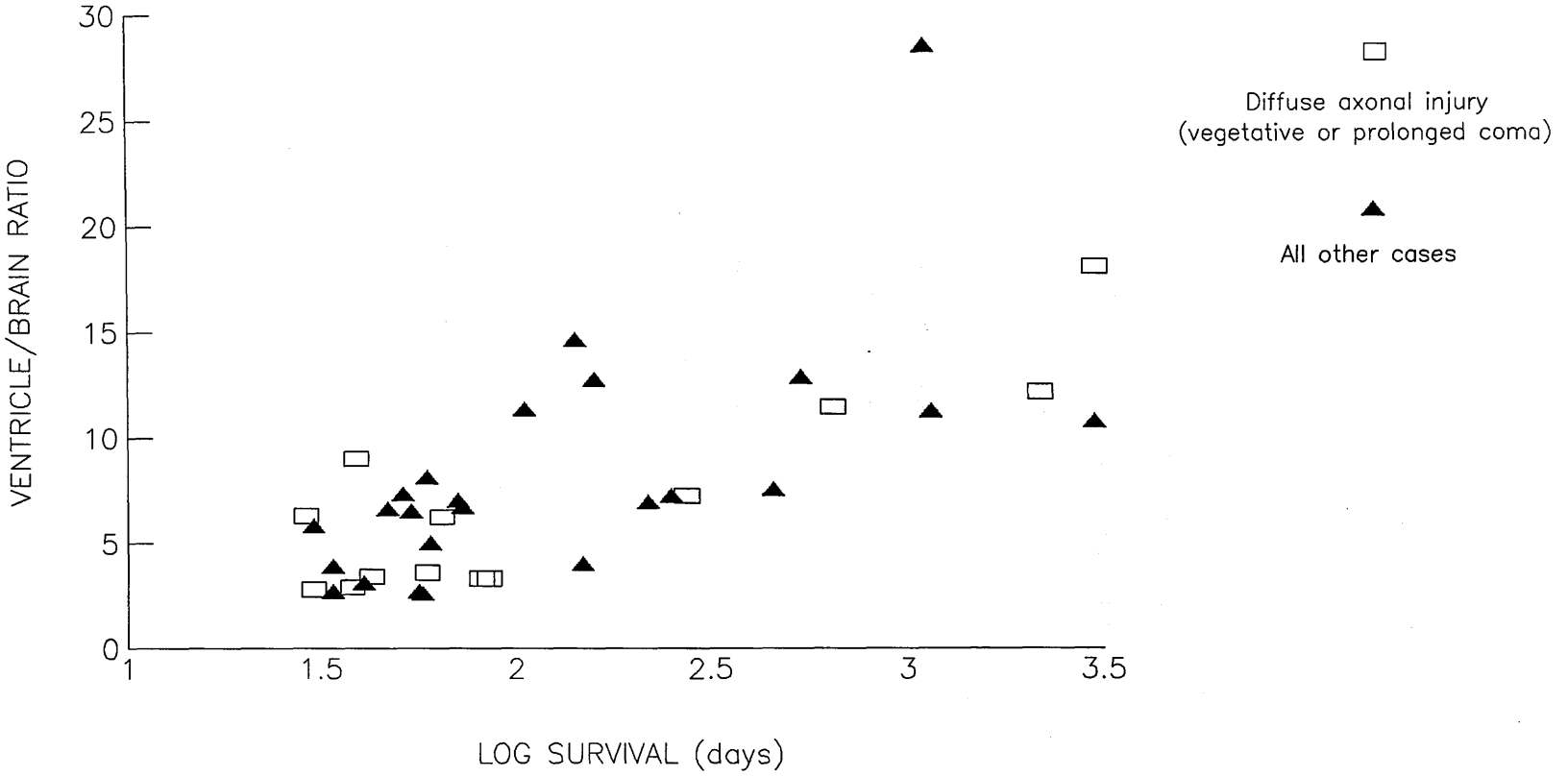


Fig. 10.1

Scatter diagram showing relationship between ventricle/brain ratio and duration of survival expressed as log. survival (days). Cases in which diffuse axonal injury was associated with a vegetative state or prolonged coma are indicated separately.

of diffuse hypoxic brain damage (No. 42; Fig. 8.1). The next highest VBR's, ranging from 11.4 to 18.0, were found in six consecutive cases of diffuse axonal injury (Nos. 32, 34, 40, 41, 44 and 46) (Fig. 6.4). In a few cases of long survival with diffuse lesions, marked cerebral atrophy was a feature (e.g. Fig. 6.5 and 8.1). These findings suggest that loss of cerebral parenchyma was an important cause of ventricular dilatation.

Ventricular drainage had been carried out in four patients, in three of whom this had been temporary. In the fourth case (No. 16), a clinical diagnosis of obstructive hydrocephalus had been made on the basis of enlargement of the ventricles seen radiologically after treatment of a combined extradural/subdural abscess which developed at a craniotomy site. A ventriculo-peritoneal shunt had been inserted but without any clinical improvement. At post-mortem examination there was thickening of the meninges in the basal cisterns and at the exit foramina of the fourth ventricle. Mild hydrocephalus was present (Fig. 5.1). Focal meningeal thickening or adhesions were common in this series but their significance is difficult to assess. The aqueduct was patent in every case. Apart from Case No. 47 (see below) there were no cases in which raised intracranial pressure was thought, after dissection, to have contributed to death.

Rare complications of late onset

Two severely disabled patients worsened neurologically some time after they had attained their maximal recovery. One of these (Case No. 47, survival 14 years 3 months) suffered from

hypertension and his step-wise deterioration over several years was attributed clinically to cerebrovascular disease. The cause of death was massive cerebellar haemorrhage. There was flattening of the cerebral convolutions associated with moderate hydrocephalus consistent with an obstructive aetiology. Dissection of the brain also demonstrated several lacunar infarcts. In the other case (No. 43) the features of both central pontine myelinolysis and Marchiafava-Bignami disease were found on post-mortem examination. A further case of interest in this context was a vegetative patient (Case No. 44) for whom no history of neurological deterioration was obtainable although the brain and spinal cord harboured the classic histological changes of pellagra. These last two cases will be described in more detail below, since they are examples of rare metabolic or nutritional diseases. These were probably complications of debilitation and malnutrition rather than trauma.

Central pontine myelinolysis and Marchiafava-Bignami disease in a severely disabled patient

Case history

This 46 year old man (Case No. 43) was assaulted with a concrete slab and sustained severe craniofacial injuries including fractures of the facial bones, the base of the skull and the occiput. He was admitted unconscious to the Institute of Neurological Sciences. A right intratemporal haematoma was

identified on CT scanning but was managed conservatively. After repair of his craniofacial injuries, the patient was discharged to another hospital for long-term care. He was completely blind due to optic nerve damage, was unable to walk without assistance and was apathetic and uncommunicative. His care was hindered by aggressive disinhibited behaviour for which he required to be sedated. Eighteen months after the injury the patient became increasingly disorientated, confused and violent towards patients and ward staff. His appetite was described as voracious. This state of affairs persisted until some 3 years after his injury when over a period of 6 weeks he became progressively "stuporose" (the expression in the case record), and developed a flat toneless speech and increasing difficulty in swallowing. A clinical diagnosis of bulbar palsy was made but a neurological opinion was not sought and no investigations were carried out. On some occasions the patient vomited. Oral fluid intake was poor, but there was no parenteral administration of fluids. Serum electrolytes were not measured. He deteriorated progressively, becoming comatose with clinical evidence of bronchopneumonia, and died three years and two months after his original injury.

Post-mortem examination

General: The body was that of a slimly built male with various facial scars. There was pulmonary oedema and bilateral basal pneumonic consolidation. Several small abscesses were present

in the cortex of the right kidney. The other organs appeared healthy.

Neuropathology: The healed site of an old bone flap was identified in the skull. The brain weighed 1120g. There were old bilateral frontal, right temporal and right parietal contusions (TCI = 21). Coronal sections demonstrated a small old haematoma in the right temporal lobe. There was moderate symmetrical enlargement of the lateral and third ventricles. The corpus callosum was thin but no focal lesion was seen. The interventricular septum was deficient at one point. The cerebellum was normal. The brain stem appeared normal externally and on section and, in particular, there was no focal lesion or any evidence of demyelination.

Histology: The presence of old contusions and an old haematoma was confirmed. Serial blocks of the entire corpus callosum were examined histologically. In one of these, at the level of the hypothalamus and predominantly in the upper half of the corpus callosum, there was a well demarcated zone of demyelination (Fig. 10.2). Between this and the superior surface of the corpus callosum there was a narrow layer of spared myelin. Within the lesion there were numerous lipid-laden macrophages and reactive astrocytes (Fig. 10.3a), but on silver staining there was preservation of axons (Fig. 10.3b). There were no other foci of demyelination in the cerebral hemispheres or cerebellum.

In the brain stem there was a symmetrical zone of demyelination in the basis pontis, centred on the median raphe (Fig. 10.2). As with the callosal lesion, lipid-laden macrophages and reactive astrocytes were present in abundance (Fig. 10.4a), but neurons were spared and on silver staining an apparently normal complement of axons traversed the lesion (Fig. 10.4b). In frozen sections there was scanty positivity on Oil Red O and Marchi staining within the demyelinated area. There was no focal lesion of the type associated with diffuse axonal injury.

Comment

In this case, the only lesions of primary traumatic origin were focal in nature and comprised cerebral contusions and a small intracerebral haematoma. There was no evidence of diffuse axonal injury. The lesions present in the corpus callosum and the pons were similar histologically, and consisted of zones of essentially peri-axial demyelination with florid reactive features and no evidence of previous haemorrhage. This combination of features would not be seen in the focal lesions of diffuse axonal injury, particularly at this length of survival (three years and two months). The callosal lesion was highly suggestive of Marchiafava-Bignami disease, but was unusual in being confined to only one level although it is recognised that only a portion of the corpus callosum may be involved (Brion, 1975). The pontine lesion, however, was characteristic of central pontine myelinolysis. The

topographical and histological features were quite unlike those of either the focal lesions of diffuse axonal injury or Wallerian degeneration, particularly when the duration of survival is taken into account.

Pellagra in a vegetative patient

Case history

This 26 year old man (Case No. 44) was the driver of a car which skidded off the road and crashed. He had been rendered unconscious at the time of the injury and remained so on admission to hospital. There were virtually no abrasions or lacerations to the head and there was no fracture of the skull. Other injuries included fractures of the distal shaft of the left femur and the right fifth metacarpal bone. The patient never regained consciousness but about four weeks after the accident he began to open his eyes spontaneously. He required to be fed by nasogastric tube. When seen 12 months after the injury he was lying with his eyes wide open, almost staring, and occasionally with brow furrowed. There was a gross right hemiplegia including the face. Both legs were extended but were capable of some flexion response. He made chewing movements but still required to be tube-fed. There was apparently no improvement before the patient died some 6 years after the injury. The case notes had been discarded and the only information gleaned about his terminal illness was that he had developed a chest infection.

Post-mortem examination

General: The body was that of an extremely emaciated young man. There were marked flexion deformities of the upper limbs and the left leg was flexed, adducted and externally rotated. There were several large decubitus ulcers in the lumbo-sacral and gluteal regions. No other cutaneous lesions were noted in the autopsy report. The heart (250g), liver (800g), kidneys (100g and 95g) and spleen (50g) were small but otherwise normal. On dissection of the lungs there was an acute purulent bronchitis.

Neuropathology: The skull and meninges were normal. The brain was small (1020g) and there was striking generalised atrophy with widening of sulci. There was a single small contusion (TCI = 3) of the left frontal lobe. Serial coronal sections of the cerebral hemispheres showed that there was bilateral demyelination and cystic change of the white matter extending down from the superior and middle frontal gyri into the centrum semiovale. This was particularly obvious in the anterior third of the cerebral hemispheres. There were small sulcal infarcts in the depths of the superior and middle frontal sulci, and in the insulae. The corpus callosum was very thin throughout its length and contained an orange brown pigmented scar to the left of the midline. The interventricular septum was intact. The internal capsules were attenuated. The thalamus was shrunken on both sides with cystic change on the left side. There was a small scar in the medial segment of the left globus pallidus.

The left hippocampus was sclerosed and previous tentorial herniation was indicated by bilateral old wedge pressure necrosis in the parahippocampal gyri. The lateral and third ventricles were moderately enlarged and symmetrical.

The cerebellar hemispheres were atrophic and on section there was demyelination which appeared to be more extensive on the left side than on the right (Fig. 6.5).

The brain stem was greatly reduced in size and on section there was marked enlargement of the aqueduct and fourth ventricle. The tegmentum of the pons was small but there were no focal lesions in the dorsolateral quadrants. In the medulla there was uniform reduction of the long fibre tracts and apparent hypertrophy of the inferior olivary nuclei. The pyramids were reduced in size with evidence of demyelination.

The spinal cord was normal externally and at multiple representative levels.

Histology: The features seen on gross examination were confirmed to be present. There was widespread gliosis and demyelination (Fig. 6.4). Asymmetrical demyelination and gliosis affected various tracts in the brain stem. In addition to the focal lesion seen in the corpus callosum, a focus of gliosis and haemosiderin deposition was identified microscopically in the left superior cerebellar peduncle. Thus, the classic triad of diffuse axonal injury was fulfilled. There were microscopic lesions of diffuse vascular injury in white matter, in various basal ganglia, and in the subiculum of the

left pes hippocampi and hippocampus. Thalamic shrinkage and gliosis with marked rarefaction of the dorso-medial nucleus on the left side was considered to represent retrograde degeneration secondary to diffuse axonal injury. Sections of the spinal cord showed asymmetrical demyelination in the descending corticospinal tracts.

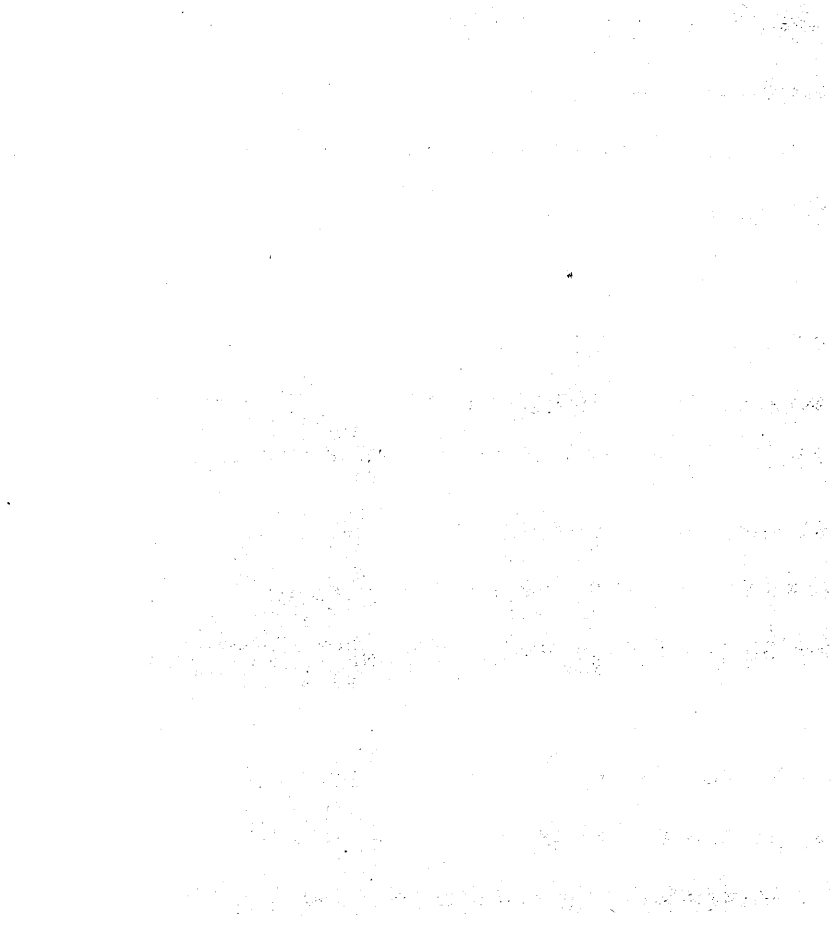
As evidence of secondary brain damage, bilateral old wedge pressure necrosis was confirmed to be present. There was marked atrophy of the medial portions of the superior cerebellar cortex. This was attributed to subtotal ischaemia within the distributions of the superior cerebellar arteries. This was the only evidence of ischaemic brain damage. There was no evidence of diffuse hypoxic brain damage.

In addition to the above lesions, there was the unexpected finding of widespread central chromatolysis. This was most striking in the Betz cells of the motor cortex (Fig. 10.5a) and the pontine nuclei (Fig. 10.5b), but was also present in the dorsal nuclei of the vagi, the region of the nucleus ambiguus and, less certainly, in the gracile and cuneate nuclei and the mesencephalic nuclei of the fifth cranial nerves. In the spinal cord, scattered anterior horn cells also appeared to show central chromatolysis.

Comment

The main traumatic lesion in this case was extensive diffuse axonal injury. The additional finding of widespread central chromatolysis was diagnostic of pellagra affecting the central

nervous system. Demyelination of the the posterior columns of the spinal cord has also been described in pellagra but was not present in this case. Central chromatolysis may be seen occasionally in cases of diffuse axonal injury but only in the earlier stages, at about three or four weeks survival (Strich, 1969). Central chromatolysis was not seen in this series apart from the above case.



CHAPTER 11

DISCUSSION

The nature of brain damage underlying a poor outcome in patients of prolonged survival after head injury has been the subject of numerous investigations. These have been summarised in the review of the literature. The most important studies include the seminal work of Strich (1956, 1961) and the large series of Jellinger and Seitelberger (1970). Strich (1956,1961) concentrated on one type of brain damage, and established the concept of diffuse degeneration of the white matter as a cause of coma and severe post-traumatic dementia. Strich believed that the initial impact was responsible for the damage to the white matter in this process. Jellinger and Seitelberger (1970), on the other hand, expressly denied that this could be the only cause of persistent deep coma or coma vigile, and instead maintained that lesions of the brain stem are the most important factor determining the outcome of head injuries. In their view, the diffuse degeneration of Strich is at least in part due to vascular effects and oedema.

In the past, clinical terms for abnormal states of consciousness and recovery after head injury tended to be idiosyncratic and imprecise, including the expressions "post-traumatic dementia" and "post-traumatic encephalopathy" coined respectively by Strich (1956) and Jellinger and Seitelberger (1970) to embrace the clinical features of their cases.

Terminology has since been placed on a more even footing by Jennett and his colleagues. The Glasgow Coma Scale (Teasdale and Jennett, 1974) is widely used and its definition of coma (Teasdale and Jennett, 1976; Jennett and Teasdale, 1977) is said to minimise ambiguity (Teasdale, 1986). Similarly, there is increasing use of the Glasgow Outcome Scale (Jennett and Bond, 1975) which includes as one of its categories the persistent vegetative state as earlier characterised by Jennett and Plum (1972) and now known simply as the vegetative state (Jennett et al., 1977b). It should be borne in mind that these are clinical scales dealing with levels of consciousness and function, and were intended to reflect the overall severity of brain damage rather than indicate the type or anatomical locus of any lesion(s) present.

In an autopsy study of considerable epidemiological value, Adams et al. (1980a) undertook a comprehensive analysis of all the lesions present in a consecutive series of head injuries. Clinico-pathological correlation was not one of the aims of this study, and all patients were included regardless of duration of survival, which for the vast majority ranged from 12 hours to 14 days. Adams et al. (1980a) concluded that the lesions most commonly associated with a fatal outcome are diffuse axonal injury, hypoxic brain damage and secondary damage to the brain stem. No previous survey has adequately analysed in a similar fashion the range of lesions underlying a poor outcome after head injury in a population defined according to clinical criteria. The work presented in this thesis is an attempt to

fill this gap in the literature. It was decided to restrict the series to patients who were vegetative, severely disabled or in prolonged coma, primarily because of the rarity of autopsy material from patients of better outcome. A lower survival limit of 28 days was chosen since this is probably the earliest at which allocation on the Glasgow Outcome Scale is possible (Jennett et al., 1977a), although it is recognised that this may be difficult, for example, in the case of vegetative patients (Braakman, 1984). It has been shown, however, that the majority of patients have reached their final state on the Outcome Scale within three months of the injury (Jennett et al., 1977a). In the present series, less than half the patients lived for more than three months, and it is possible that some, particularly those of shorter survival, might have improved to some extent had they lived longer.

In clinical practice, severely disabled patients greatly outnumber those in a vegetative state (Jennett et al., 1977b). In the present series, however, the majority of patients were vegetative. Of those classified as severely disabled, only two were ever able to return home. Thus, the series is weighted towards the worse end of the spectrum of disability after head injury. This is explained by the derivation of the cases from an autopsied hospital-inpatient population. Apart from this, the demographic and clinical characteristics of this series are broadly similar to those found by Jennett et al. (1977b) when they followed the progress of a large number of patients for at least six months after severe head injury. Although many died

within the first three months, and the survivors included all grades of recovery, the data are of interest since they are representative of the pool of severe head injuries from which vegetative and severely disabled patients are drawn. The data from the two series are compared in Table 11.1. The main

Table 11.1

Comparison of demographic and clinical features in two series of patients with severe head injuries.

	Jennett et al. (1977b)	Thesis
Type of series	Clinical	Autopsy
n	424	48
Survival	6 hrs-6 months	over 1 month
Age (mean)	34	38.8
Sex ratio (m:f)	4.3:1[1]	4.3:1
RTA (all)	53%	56%
(pedestrian only)	24%	14%
Falls (all)	25%[2]	27%
Assaults	19%	17%
Extracranial injuries	30%	35%
Lucid interval (complete or partial)	32%	19%
Fracture of skull	77%	54%
Intracranial haematoma (any type)	51%	54%

1 Based on 695 cases from 3 centres
2 Refers to "work related injuries" plus drunken falls

differences are the lower proportion of road traffic accidents involving pedestrians (and, by implication, a higher proportion involving vehicle occupants), a lower incidence of a lucid interval (whether complete or partial), and a lower incidence of fracture of the skull in the present study. The slightly older mean age in the present study may reflect the greater powers of recovery of younger patients, as shown by Teasdale et al. (1982), rather than an increased death rate.

Miller et al. (1978) investigated the occurrence of systemic insults on admission to hospital in patients with severe head injuries. They found hypoxia in 30% of patients and arterial hypotension in 13%. In the present study there was hypoxia in 35% and arterial hypotension in 29%. Although similar criteria were employed, the data are not quite comparable since those of Miller et al. (1978) were obtained on admission.

Fractures of the skull were present in 54% of cases in the present study, a figure which is similar to that of Jellinger and Seitelberger (1970) (52%), but is less than found by Jennett et al. (1977b) (77%) or Adams et al. (1980a) (79%). Any discrepancy cannot be attributed to greater difficulty in recognising fractures with the lapse of time from the injury since the results of clinical investigations were taken into account in this study, although comparison of clinical and post-mortem data showed that after several weeks fractures were less likely to be identified.

Cerebral contusions were the most common lesion in the present series, occurring in 90% of cases, which compares well

with the figure of 95% found by Adams et al. (1980a) who used a similar method to quantify contusions. Thus contusions are confirmed to be a common occurrence, but it is of interest that in 10% of cases in the present study this hallmark of a head injury was absent. A mere statement of the frequency of contusions is of little worth without an assessment of severity. Adams et al. (1980b) were probably the first to devise a practical quantitative method for the analysis of contusions, and their "contusion index method" in either its original or slightly modified form has now been applied to series of both human and primate brains (Adams et al., 1980a, 1980b, 1985b). The contusion index method was repeated in the present study in order to test the conclusions of Adams et al. in another group of patients, and also to allow comparison with similarly analysed material from a larger series (Adams et al., 1980b, 1985b). In the present study the median total contusion index was 13, similar to the figure of 17 quoted by Adams et al. (1985b). Contusions were most common in the frontal and temporal lobes, as found by Adams et al. (1985b). The severity of contusions in these and also the other anatomical locators was very similar to that found by Adams et al. (1985b). When contusions in the present series were arbitrarily graded as mild, moderate or severe (based on total contusion indices), it became apparent that the source of the difference in grade was the severity of frontal and temporal contusions, whose median contusion indices underwent a several-fold increase between the mild and severe grades. This selectively severe involvement of

the frontal and temporal lobes was noted by Adams et al. (1985b). These authors also demonstrated that contusions are more severe in patients with a fracture of the skull than without a fracture. The present study confirmed this and further showed that contusions were particularly severe in cases with haematomas in addition to fractures. In general, the contusions in this series appear to have characteristics similar to those which have been described previously in patients of shorter survival after head injury.

Intracranial haematomas in this series were classified according to whether or not they were evacuated, mainly because this was a practical way of assessing size and clinical importance retrospectively, but also because this enabled comparison with other series. Haematomas (whether or not evacuated) had been present in 54% of cases in this series, and had been evacuated in 44% of cases. In their clinical series, Jennett et al. (1977b) quote an incidence of 51% for haematomas, the great majority of which had been evacuated neurosurgically. In the series of Jellinger and Seitelberger (1970), however, there were haematomas in 40% with evacuation in 33% of cases, while Adams et al. (1980) gave an incidence of 64%, the great majority of which had been evacuated. Haematomas, whether taken overall or as evacuated only, were associated with fractures of the skull. Cerebral contusions were more severe in patients with an intracranial haematoma than without, although when the interrelations between fractures, haematomas and contusions were analysed, a fracture of the skull seemed to be the factor most

closely linked to severity of contusions. The median total contusion indices were similar whether there were contusions alone or together with intracranial haematomas, but increased markedly in the presence of a fracture of the skull and were most severe in cases with the combination of a fracture and an intracranial haematoma. In this series, fractures and haematomas did not occur apart from contusions. Thus, those lesions which were classified as primary and focal in type tended to occur together.

Lesions such as contusions and haematomas are in general easily recognised by the naked eye at post-mortem examination, although haematomas may be absorbed with time. There is no doubt that, along with fractures, they are engendered or, at least in the case of haematomas, initiated at the moment of impact. In cases with diffuse axonal injury, on the other hand, the brain often looks remarkably normal. Again, there has been much disagreement in the literature regarding the aetiology of diffuse axonal injury, particularly over whether it is primary or secondary in origin. The diagnosis of diffuse axonal injury is essentially histological. Even then, although various features can be recognised with ordinary haematoxylin and eosin or myelin stains, they are considerably enhanced by the use of appropriate special stains. An example is the Wallerian degeneration which is such a dramatic feature in cases of intermediate survival. Even when extensive, its severity can only be appreciated when a method such as the Marchi technique is used to identify degenerating myelin (Strich, 1956). Retraction ball

formation is best seen in silver preparations. It is perhaps partly for these reasons that the general recognition of diffuse axonal injury was so long delayed compared with the more obvious types of brain damage. It was thus not until 1956 that Strich published her pioneering paper on "diffuse degeneration of the cerebral white matter". Later, Strich (1961) enlarged her series and pointed out that the most striking feature in cases of shorter survival was large numbers of retraction balls. Mitchell and Adams (1973) approached the recognition of primary brain injury from another direction. They appreciated that the clinical syndrome of primary brain-stem injury could also be caused by haemorrhage or infarction in the brain stem secondary to the effects of a high intracranial pressure, and that there was a corresponding neuropathological difficulty in making the distinction between primary and secondary lesions in the brain stem. Secondary changes could, for example, mask underlying primary lesions.

Using histological criteria, such as pressure necrosis in the parahippocampal gyri or cingulate gyrus and necrosis of the medial occipital cortex, to exclude cases in which there had been a high intracranial pressure, Mitchell and Adams (1973) were able to isolate a group of cases with lesions in the brain stem which could only be attributed to impact and were therefore unequivocally primary in type. In each case these comprised a focal lesion in the superior cerebellar peduncle and evidence of axonal damage or long-tract degeneration, depending on the length of survival. In all these cases, however, it was found

that abnormalities were not confined to the brain stem but were also present elsewhere in the brain and always included a focal lesion in the corpus callosum. In an enlarged series (Adams et al., 1977), the diagnostic importance of the focal lesions was emphasised, particularly since these were often visible macroscopically. Similar lesions had been present in the cases of Strich (1956), but Adams et al. (1982) endowed them with new significance by introducing the concept of a diagnostic triad. Diffuse axonal injury was defined as focal lesions in (1) the corpus callosum, and (2) the dorsolateral quadrant of the rostral brain stem, together with (3) microscopic evidence of diffuse damage to white matter. Abandoning the lack of evidence for a high intracranial pressure as a prerequisite, Adams et al. (1982) used the diagnostic triad to identify cases of diffuse axonal injury and characterise their clinical and pathological features. In cases of diffuse axonal injury, compared with controls, there was an absence of a lucid interval; a higher incidence of road traffic accidents; a lower incidence of falls; there were fewer fractures of the skull and intracranial haematomas; less severe contusions; a lower incidence of pressure necrosis in the parahippocampal gyri; and a similar incidence of hypoxic brain damage. This was the first attempt to analyse the features of diffuse axonal injury objectively, but it has since become clear that focal lesions in the corpus callosum and dorsolateral quadrant of the rostral brain stem are not essential to make the diagnosis. Adams et al. (1985a) have now described several cases of diffuse axonal injury which

lacked any focal lesions in the classic sites, and would have been unsuspected without histological examination. It was in the light of this experience that for the purposes of the present study it was decided not to base the diagnosis of diffuse axonal injury on focal lesions but instead to revert to purely histological criteria. Diffuse axonal injury was considered to be present whenever there was widespread evidence of axonal damage as shown by retraction balls, Wallerian degeneration or demyelination which could not be attributed to any proximal lesions. In the present study, diffuse axonal injury as thus defined was second in frequency to contusions only, being present in 52% of cases. This is a considerably higher proportion than the 13% found by Adams et al. (1980a) in their consecutive series, and also higher than the approximation of one third of cases in the experience of Strich (1956). The reasons for these discrepancies will be addressed below, but differences in definition are unlikely to be of major importance. Seven of the 25 cases in this study would not have conformed to the classic triad, but even if these had been excluded, the incidence of diffuse axonal injury would have been 38%, three times that found by Adams et al. (1980a). All the cases would presumably have been acceptable to Strich (1961). In the present series, the other pathological findings in cases of diffuse axonal injury corresponded to those found by Adams et al. (1982) in that there were fewer fractures and intracranial haematomas, less severe contusions, and pressure necrosis was less frequent than in cases without diffuse axonal injury.

Jellinger and Seitelberger (1970) claimed that moderate to severe "white matter degeneration" was present in about two-thirds of their cases of prolonged post-traumatic encephalopathy. However, it is not clear what these authors mean by white matter degeneration. With this term, Jellinger and Seitelberger appear to make reference to the work of Strich (1956) whom they quote in this context, but in their hands it seems to denote two distinct lesions of white matter. These comprise firstly, diffuse demyelination in the vicinity of traumatic defects and, secondly, diffuse degeneration of the white matter of the cerebral hemispheres resulting in incomplete loss of axons and their myelin sheaths and ranging histologically from retraction ball formation to diffuse demyelination and cavitation of the centrum semi-ovale. It is only the latter type which appears to correspond with diffuse axonal injury as it is generally understood. Jellinger and Seitelberger (1970) point out that in the analysis of cerebral trauma a distinction should be made between primary lesions caused by direct mechanical effects at the moment of injury, and secondary or "reactive" lesions which develop post-traumatically as a result of circulatory changes. Secondary lesions are said to include not only local changes surrounding mechanical lesions, but also focal and diffuse brain damage, the location and extent of which is highly independent of the immediate sequelae of trauma, and caused by cerebral and peripheral circulatory disorders, post-traumatic oedema and increased intracranial pressure. Jellinger and Seitelberger list diffuse

degeneration of the white matter under the heading of secondary brain damage and state that it is a consequence of severe cerebral oedema. In support of this contention they point out that cerebral oedema is common in cases of shorter survival and that white matter lesions are frequently combined with vascular and anoxic damage to the cortex and basal ganglia. On the other hand, Jellinger and Seitelberger concede that physical damage to nerve fibres may be one of the factors underlying diffuse white matter degeneration in cases of post-traumatic encephalopathy, citing as evidence of primary damage the occurrence of small "tears" and haemorrhages in the white matter. Thus, it is concluded that post-traumatic degeneration of white matter is due to a "very complex effect of degenerative changes secondary to mechanical alterations and vascular and/or oedematous lesions". Secondary lesions undoubtedly occur in cases of diffuse axonal injury. In the present series, for example, there was hypoxic or ischaemic damage in 32% of cases and pressure necrosis in the parahippocampal gyrus in 44% of cases. Adams et al. (1982) found hypoxic or ischaemic damage in 49% and brain swelling in 16% of their cases of diffuse axonal injury, similar to the incidence of these features in cases without diffuse axonal injury, and pressure necrosis in the parahippocampal gyrus in 56%, less often than in cases without diffuse axonal injury. Graham et al. (1987) found diffuse axonal injury in 41% of a series of cases without evidence of a high intracranial pressure. It is thus clear that diffuse axonal injury often occurs in the absence of significant hypoxic

or ischaemic damage or brain swelling. More telling evidence against any role for secondary phenomena in the pathogenesis of diffuse axonal injury has now accrued from an experimental model. Gennarelli et al. (1982) have succeeded in reproducing diffuse axonal injury in primates by accelerating the head without impact, and have stressed the absence of hypoxic or ischaemic damage in the neocortex or cerebellum, and the absence of hypoxaemia.

Analysis of the frequency and type of focal lesions in the corpus callosum and dorsolateral quadrant of the rostral brain stem in the cases of diffuse axonal injury in the present series showed that macroscopic lesions in both sites were present in 52% of the cases and that, including microscopic lesions, the diagnostic triad of Adams et al. (1982) was fulfilled in only 72% of the cases. It may be argued that the passage of time may have obscured small lesions, but it is unlikely that they would have escaped detection in a careful microscopic examination of corpus callosum and brain stem. In any case, the greater frequency of focal lesions in the corpus callosum than in the dorsolateral quadrant of the rostral brain stem is in keeping with experimental findings. Gennarelli et al. (1982) showed in their primate model of diffuse axonal injury that focal lesions occurred preferentially in the corpus callosum, and that with increasing clinical severity, as judged by length of post-traumatic coma and quality of survival, focal lesions also appeared in the brain stem. This formed the rationale for a numerical grading of diffuse axonal injury, viz. grade 1 (least

severe) - no focal lesions present; grade 2 - a focal lesion in the corpus callosum but not in the region of the superior cerebellar peduncle; and, grade 3 (most severe) - focal lesions in both the corpus callosum and the region of the superior cerebellar peduncle. On this basis, and using the same criteria, grading of diffuse axonal injury was carried out in the present study. The majority of cases, 72%, were classified as grade 3, 24% as grade 2, and 4% as grade 1. While it may be suspected that this system is rather crude, it did appear to have clinical relevance in that there was a relation between outcome and grade of diffuse axonal injury. An ideal method of grading the severity of diffuse axonal injury would directly quantify the amount of white matter damage. This, however, poses formidable logistic problems, not only due to changes in histological appearances with the passage of time, but also because the distribution of the features varies considerably between cases and within the individual brain. Thus it is common to find that the diffuse axonal injury is asymmetrical, or involves one tract with sparing of an adjacent tract, or one level of the brain stem but not another. The significance of Marchi positivity is particularly difficult to assess at either extreme of the period of time over which this occurs, and the quantification of rarefaction of white matter, or demyelination, or gliosis, is extremely subjective.

Another feature found by Strich (1956, 1961) in her cases of diffuse degeneration of the white matter was an inconspicuous astrocytic reaction consisting of a few plump astrocytes and

occasional clumps of glial cells or glial stars. Adams et al. (1977) comment on the presence of numerous microglial stars in their cases of diffuse brain damage of immediate impact type. In the present study, they were a constant features of cases of diffuse axonal injury of up to 18 months survival, but were also found in 17 of 20 cases without diffuse axonal injury within the same period. A distinguishing feature was that in the cases with diffuse axonal injury, microglial clusters were much more numerous and tended to have a characteristic distribution. They tended to occur in superficial rather than deep white matter, to be medial rather than lateral and superior rather than inferior in the cerebral hemispheres. There was therefore a marked predilection for the parasagittal white matter, corresponding to the areas of maximum demyelination seen in other cases of diffuse axonal injury in this series. In cases without diffuse axonal injury, microglial clusters were scanty and appeared to be randomly distributed.

Both Clark (1974) and Oppenheimer (1968) found microglial clusters to be common after a head injury, but their investigations were based on unselected cases of various survivals and clinical outcomes including some who had recovered from brief concussion (Oppenheimer) and fully conscious patients (Clark) as well as cases of more severe brain damage. These observations, and the presence of microglial clusters in cases from the present study without other features of diffuse axonal injury, might suggest that there is a spectrum of diffuse axonal injury in which the milder forms are characterised by microglial

clusters only. Microglial clusters, however, are not specific for head injury, as suggested by Oppenheimer (1968), but have also been associated with hypoxic brain damage (Mitchell and Adams, 1973), viral diseases of the nervous system and neuronal degeneration of unknown aetiology such as motor neuron disease (Brownell and Tomlinson, 1984). Thus microglial clusters seem to be a non-specific reaction to some types of white matter damage, and there may be reasons other than trauma for the occurrence of occasional microglial clusters in cases without diffuse axonal injury.

Small lesions apparently of vascular origin are common in diffuse axonal injury. Strich (1956) noted small haemorrhages and softenings in white matter, small cortical infarcts at the bottom of sulci, and sclerosis of the hippocampi. Jellinger and Seitelberger (1970) described, as aspects of white matter degeneration, small focal necroses with or without haemosiderin and small perivascular necroses. (This latter type is clearly unrelated to diffuse axonal injury since the examples given include temporal and occipital lesions due to tentorial herniation and compression of the posterior cerebral arteries). Scattered small haemorrhages were described in cases of "shear injury of the brain" (i.e. diffuse axonal injury) by Peerless and Rewcastle (1967). Some of these lesions occurring in particular sites are dealt with individually in the literature. Voigt et al. (1977) investigated haemorrhagic lesions near the superior margin of the cerebral hemispheres, within the cortex or subcortical white matter, and designated these as "rotational

cerebral injuries near the superior margin of the brain". These were present in 11% of cases of head injury, but in those surviving more than one week were associated with retraction balls both around and distant from vessels. Adams et al. (1986b) used the term gliding contusions (after Lindenberg and Freytag (1960)) for lesions of this kind and found that although they also occurred in the absence of diffuse axonal injury, they were more frequent in cases with diffuse axonal injury.

Sulcal infarcts were probably included with gliding contusions by Voigt et al. (1977) and Adams et al. (1986b) but were treated separately in the present study. Although these lesions are often found together in the dorsal paramedian regions of the cerebral hemispheres, a distinction is worth making because sulcal infarcts can occur without, or distant from, gliding contusions. It is of interest that the nature of sulcal infarcts in this series had not always been appreciated previously since they had often been misinterpreted as ischaemic brain damage of boundary zone type. This is not surprising in view of the frequency of these lesions in the region of the boundary zones between the territories of the anterior and middle cerebral arteries. In this regard, it is significant that Adams et al. (1982) report that boundary-zone hypoxic damage was present in 40% of their cases of diffuse axonal injury, in marked contrast to its absence from any of the cases in the present study. The present study thus affords further evidence for the lack of significant secondary brain damage in diffuse axonal injury. Janzer and Friede (1979) have described

"perisulcal infarcts" in hypotensive patients who had not sustained a head injury, but these constituted true infarction of the cerebral cortex within sulci, accentuated in arterial boundary zones. Broelsch and Gerhard (1970) studied hippocampal lesions and found them to be common. In only a small percentage was there selective necrosis of the type associated with hypoxia: in the vast majority the lesions, which included haemorrhages, were related to vessels. Diffuse axonal injury was not taken into account by these authors.

Grčević (1982) has set forth a recurrent pattern of "primary" focal, mainly haemorrhagic, lesions which he designated as "inner cerebral trauma". This comprises lesions in the corpus callosum, septum pellucidum and fornix, tela choroidea and choroid plexus, around the ventricles, in the cingulate gyrus, and in the basal ganglia and thalamus. Collectively, Grčević emphasised, these form a butterfly pattern radiating from the lateral ventricles. This "inner cerebral trauma" is frequently associated with "outer cerebral trauma" (i.e. lesions in the parasagittal and hippocampal regions) and also with focal lesions in the brain stem, particularly the "upper lateral quadrants" of the midbrain. Grčević's work can be criticised in that it is not clear on what grounds cases with secondary lesions were excluded from his study, since he himself claims that the morphological distinction between primary and secondary lesions is virtually impossible in the hippocampal region and very difficult in the brain stem. There is no reference to degeneration of white matter except with regard to

some chronic cases of inner cerebral trauma in which periventricular lesions were associated with paraventricular demyelination and sclerosis of the type described by Strich (1956). This was regarded by Grčević as further evidence of primary damage, but aggravated by secondary phenomena (oedema and vascular disturbance) as part of a process of "post-traumatic cerebral disease".

In the present series there was a strong relation between diffuse axonal injury and sulcal infarcts, gliding contusions, multiple vascular lesions in the white matter, and vascular lesions in the hippocampi. There was a less marked but statistically significant relation between diffuse axonal injury and vascular lesions in the region of the basal ganglia. In the present series multiple vascular lesions in the white matter were most common in the temporal and frontal lobes, showing that lesions of this kind are more widely distributed in the cerebral hemispheres than Grčević (1982) indicated.

Vascular lesions thus tend to be widely scattered, but are histologically similar regardless of location. There is no reason why all these lesions should not be taken together as a single entity, whose features justify the designation of "diffuse vascular injury". It is necessary, however, to consider the specificity of vascular lesions for trauma. Fat embolism is another condition associated with multiple petechial haemorrhages in white matter, and it is possible that evidence of these could persist for long periods. Only one case of prolonged survival after fat embolism seems to have been

described in the literature (McTaggart and Neubuerger, 1970). This patient, who did not receive a head injury, was hypotensive and comatose before developing the features of fat embolism and then remained severely disabled for seven years. Neuropathological examination demonstrated extensive demyelination associated with many minute clusters of haemosiderin-laden cells, but also scattered areas of neuronal loss in the second and third layers of the cerebral cortex and in the hippocampi. The early onset of coma, the failure to make a good recovery, and the extent of demyelination are not typical of fat embolism, and the histological features at least raise the possibility of diffuse hypoxic brain damage. Major injuries were present in 35% of cases in the present series and included skeletal injuries in 33%, but in none of these was the diagnosis of fat embolism entertained clinically. Features such as gliding contusions and sulcal infarcts are prominent in diffuse vascular injury, but are not found in fat embolism. Thus neither clinical nor histological features would support a diagnosis of fat embolism, at least in the majority of cases.

The lesions of diffuse vascular injury are usually minute and (in general) unlikely to contribute materially to the clinical outcome, although it is possible that they may give rise to larger haematomas. This might account for the dorsal paramedian haematomas which originally constituted the gliding contusions of Lindenberg and Freytag (1960), and the deep intracerebral ("basal ganglia") haematomas which Adams et al. (1986a) found to be associated with diffuse axonal injury. Haemorrhagic

infarctions found in the region of the basal ganglia in two cases of diffuse axonal injury in the present series may have been of similar pathogenesis. The main significance of diffuse vascular injury, however, lies in its relation to diffuse axonal injury as shown in the present study. Adams et al. (1987) reproduced focal haemorrhagic lesions in the white matter of subhuman primates subjected to controlled angular acceleration of the head (the same process which produces diffuse axonal injury) and demonstrated by electron microscopy that there were marked morphological changes in endothelial cells close to the lesions. Diffuse vascular injury, however, does not seem to parallel diffuse axonal injury precisely: there were cases in the present series with vascular lesions in the absence of axonal injury. Similarly Gennarelli et al. (1982) in their experimental animal model describe vascular lesions in the hippocampus, analogous to those found in the present series in cases both with and without diffuse axonal injury. This may simply reflect a spectrum of severity at the milder end of which the typical lesions of diffuse axonal injury do not occur or are more difficult to identify than the vascular lesions. It may be more appropriate to think in terms of primary diffuse <u>brain</u> damage rather than simply "axonal" or "vascular" injury.

It is important in a systematic analysis of the effects of trauma on the brain to distinguish primary lesions (i.e. engendered at the moment of impact) from secondary lesions (i.e. occurring later). One important group of secondary lesions is brought about by high intracranial pressure, and post-mortem

evidence for a high pressure is thus particularly relevant to the classification of infarction in the brain or brain stem. Adams and Graham (1976) took various signs of internal shift and herniation and assessed their relation to the intracranial pressure as recorded in life. They found that necrosis in the parahippocampal gyrus is the only feature which correlates closely with a significantly high intracranial pressure. Lindenberg (1955) appears to have originated the term "pressure necrosis" for this lesion, and Klintworth (1968) believed that necrosis and haemorrhage in the parahippocampal gyrus constituted unequivocal evidence of transtentorial herniation, although neither of these authors justified their observations in terms of the actual intracranial pressure as measured during life. In the present series there was pressure necrosis in one or both parahippocampal gyri in 58% of the cases. This is considerably less frequent than the 83% of cases found by Adams et al. (1980a) in their series of patients mainly surviving less than one month after injury. Whilst haematomas in general (i.e. evacuated plus non-evacuated) were not significantly associated with pressure necrosis, evacuated haematomas were, suggesting that the criterion of evacuation does provide retrospective evidence that the haematomas were large. It was of interest, however, that in the present study there were 5 cases without pressure necrosis in which haematomas had been evacuated. This may simply reflect the size of the haematomas concerned, although Adams and Graham (1976) found that some of their cases known to have had a significantly high intracranial pressure did

not exhibit pressure necrosis. One possible reason for the absence of pressure necrosis (at least at the classic site) may be anatomical variation in the size of the tentorial opening (Corsellis, 1958). Grčević (1982) had misgivings about the specificity of necrosis in the parahippocampal gyrus for an elevated intracranial pressure and believed that in some cases this was another manifestation of "outer cerebral trauma" (i.e. primary brain damage). This is possible, but in the present study necrosis in the parahippocampal gyrus was present only in a minority of cases with diffuse axonal injury (especially after exclusion of those with a concomitant evacuated haematoma). Brain swelling is known to occur with diffuse axonal injury (Adams et al., 1982) and is one possible cause of a high intracranial pressure in these cases.

It is common to find allusions to the difficulty of distinguishing primary and secondary lesions in the brain stem (e.g. Bricolo and Rizzuto, 1976; Rosenblum et al., 1981; Grčević, 1982; Jellinger, 1983). The lack of diagnostic criteria has tended to produce confusing and rather arbitrary classifications of brain-stem lesions. Bricolo and Rizzuto (1976) addressed the problem in a series of 25 post-traumatic patients who survived from 2 days to 7 years in a comatose or "apallic" state. Lesions in the brain stem were found in 84% of the cases, and included "haemorrhages, softenings, nerve-fibre lesions, and infections". Only 24% of the cases were thought to represent primary brain-stem damage of the type described by Mitchell and Adams (1973): there was damage to the superior

cerebellar peduncles with similar lesions in the corpus callosum in half of the cases, although typical secondary lesions were also said to be present. The brain-stem lesions in the remaining cases of Bricolo and Rizzuto (1976) were regarded by them as secondary in type, despite the presence of "nerve-fibre lesions" and lesions in the corpus callosum in almost all of these cases. These authors concluded that brain-stem damage is mainly of secondary origin even in those patients in whom immediate loss of consciousness suggests a primary lesion of the brain stem. Peters and Rothemund (1977) examined 20 cases of the "apallic" syndrome and found that in all of these there were brain-stem lesions, the majority of which were "clearly" of a secondary nature: a major factor in this interpretation seems to have been co-existent evidence of tentorial herniation. Jellinger and Seitelberger (1970) identified brain-stem lesions in 83% of their cases of protracted post-traumatic encephalopathy. A secondary origin for the majority of these was considered to be in keeping with the frequency of evidence of raised intracranial pressure. In the same paper, Jellinger and Seitelberger distinguished two types of secondary brain-stem damage. These were respectively focal and diffuse. Focal lesions were present in 65% of their patients with protracted post-traumatic encephalopathy. The structures involved were the floor of the third ventricle and periaqueductal grey matter (in 6%), these sites plus lesions elsewhere in the brain stem (in 31%), and the tegmentum of the pons and midbrain (in 30%). The tegmental lesions evidently included "superficial softenings" in

the dorsolateral tegmentum and tectum of the mid-brain including the quadrigeminal plate, the rostral pontine tegmentum including the velum medullare anterius and the dorsolateral tegmentum. Jellinger and Seitelberger proffered the explanation that these lesions were due to compression by the free edge of the tentorium. While their small size and peripheral distribution were contrasted with the large central lesions found in acute cases, this was simply taken as evidence for different factors in the production of these different types of "secondary" lesion. The other type of secondary brain-stem lesion identified by Jellinger and Seitelberger (1970) was characterised by diffuse gliosis, particularly in the tegmentum, and which they called "glial dystrophy". The cause of this was again assumed to be raised intracranial pressure although comparisons were also made with central pontine myelinolysis, which was thought to be a related process. Each of the types of lesion identified by Jellinger and Seitelberger (1970) has been described in diffuse axonal injury. The distribution of the focal lesions corresponds to that found in diffuse axonal injury, and it is likely that the glial dystrophy was in fact related to long-tract degeneration as a result of diffuse axonal injury. It is difficult to avoid the conclusion that Jellinger and Seitelberger (1970) not only misunderstood the mechanisms underlying primary and secondary lesions but, more importantly, failed to recognise the changes of diffuse axonal injury in the brain stem. Unfortunately for purposes of comparison, their data may well have included genuine secondary

lesions in the brain stem. Jellinger in his more recent publications (1977, 1983) continues to emphasise the role of secondary brain-stem lesions in the great majority of cases of the apallic syndrome.

It is clear that the most important factor in the interpretation of focal lesions in the brain stem is the presence or absence of diffuse axonal injury. Diffuse axonal injury is associated with a particular type and pattern of focal lesions, often haemorrhagic and usually situated in the dorso-lateral quadrant(s). Any study of traumatic brain-stem lesions which fails to take diffuse axonal injury into account, or bases interpretation solely on the presence of pressure necrosis is fundamentally flawed.

In the present study, focal lesions in the brain stem were found in the absence of diffuse axonal injury in 29% of cases, in all of which there was evidence of a high intracranial pressure. In the majority of cases the lesions were visible macroscopically, and the pattern was consistent with a secondary aetiology. The lesions in the remainder were a miscellaneous group consisting of minute foci of gliosis or infarction, only identified microscopically: these were of uncertain significance. There are no data in the literature, based on similar diagnostic criteria, with which the incidence of secondary brain-stem lesions in this study can be compared. Even the (otherwise) comprehensive study of Adams et al. (1980a) gives no indication of how commonly secondary brain-stem lesions occurred in their series.

The interpretation of hypoxic and ischaemic damage in the brain is much less contentious than for diffuse axonal injury or focal lesions in the brain stem. The definitive study is probably that of Graham, Adams and Doyle (1978), although this is based on a series of patients the majority of whom lived for less than one month after injury. Jellinger and Seitelberger (1970) also refer to hypoxic and ischaemic brain damage in their series of patients with protracted post-traumatic encephalopathy.

Diffuse hypoxic brain damage was present in 4% of the present series, similar to the figure of 5% obtained by Graham, Adams and Doyle (1978) but less than the 11% incidence in the series of Jellinger and Seitelberger (1970). Ischaemic brain damage of boundary-zone distribution was present in 10% of the cases in the present series, again similar to the incidence of 9% found by Graham, Adams and Doyle (1978); Jellinger and Seitelberger (1970) did not specify this type of lesion. In the present series there was an interesting pattern associated with ischaemic damage of boundary-zone type: there was subtotal diffuse neuronal loss from the thalamus in four of the five cases. Adams et al. (1966) described different patterns of brain damage due to systemic hypotension. These include ischaemic damage concentrated in arterial boundary zones, together with variable damage in the basal ganglia, but rarely involving the thalamus; and, generalised ischaemic damage in the cerebrum and cerebellum, sparing the hippocampi but accompanied by severe damage to the thalamus. The cases of

boundary zone ischaemic damage in the present study appear to combine features of each of these patterns. A similar distribution of damage was produced experimentally by Nicholson et al. (1970) in a hypotensive subhuman primate.

Infarction involving the territories of the principal arteries supplying the cerebrum and cerebellum was present in 35% of cases in the present study. This is similar to the incidence found by Graham, Adams and Doyle (1978) although their data are not directly comparable. Jellinger and Seitelberger (1970) found involvement of the occipital lobes in 13% of their cases. Infarction involving the basal ganglia, internal capsules or diencephalon was identified in 29% of cases in the present series, considerably less than the figure of 79%, referring to the basal ganglia and thalamus, given by Graham, Adams and Doyle (1978). Jellinger and Seitelberger (1970) found lesions in the basal ganglia in 65% of cases and in the thalamus in 40%, but commented on the difficulty of deciding whether small necroses and haemorrhages in that region were primary or secondary.

In the present series, pressure necrosis in one or both parahippocampal gyri was present in the majority of cases with ischaemic damage, an association which was statistically significant for infarction in the territory of the posterior cerebral artery, and in the globus pallidus, thalamus or internal capsule. Graham, Adams and Doyle (1978) showed pressure necrosis was more frequent in cases with ischaemic lesions in the hippocampus and basal ganglia, but was not

significantly associated with ischaemic damage in the cerebrum or cerebellum (lesions in the medial occipital cortex were excluded from their statistical analysis).

The present series is extremely heterogeneous in terms of the lesions present. It seems reasonable that clinico-pathological correlation ought to take into account both the combination of lesions present, and the severity of lesions. These are factors which have barely been considered in the past, as different authors pressed the claims of one type of lesion against another as the cause of post-traumatic disability.

Diffuse axonal injury was present in just over half the cases and constituted the most common type of diffuse brain damage. In a few cases this was the only lesion, but in the great majority of cases with diffuse axonal injury there was also contusional or ischaemic damage. The contusions, however, were mild in half of these cases, and ischaemic brain damage, when present, took the form of infarction in arterial territories or in the region of the basal ganglia, so that these additional lesions were essentially focal in distribution. There was no case in the series in which diffuse or boundary-zone hypoxic/ischaemic damage was found together with diffuse axonal injury. Strich (1956) emphasised the absence of other types of lesion from her cases of diffuse degeneration of cerebral white matter, referring in particular to fractures, haematomas and any other than trivial contusions. On the other hand, Adams et al. (1982) in their larger series of cases of diffuse axonal injury did find fractures of the skull and intra-

cranial haematomas in a proportion of cases, although less often than in cases without diffuse axonal injury, and that while contusions were often present, they tended to be less severe than in cases without diffuse axonal injury. It is likely that focal lesions are relatively unimportant in the context of diffuse axonal injury, particularly in those cases with the profound disturbance of consciousness which characterises the vegetative state or prolonged coma. When Gennarelli et al. (1982) reproduced diffuse axonal injury experimentally in subhuman primates, this was associated with coma or severe disability although the latter was defined simply as "sufficient neurological impairment to preclude eating and drinking". Gennarelli et al. (1982) devised a simple method of grading diffuse axonal injury in their animal model. When this was applied to the present series, the outcome in general was found to depend on the grade of diffuse axonal injury. The reason for this is not immediately clear, since the focal lesions in the corpus callosum and dorsolateral quadrant of the brain stem, on which the grading method is based, are small and unlikely in themselves to account for differences in the neurological outcome. The most likely explanation is that the presence of these focal lesions reflects the severity of diffuse axonal damage. Furthermore, whether a patient becomes vegetative rather than severely disabled, or a subhuman primate is in prolonged coma rather than "severely disabled" (Gennarelli et al., 1982), seems to be related to the presence of a focal lesion in the dorsolateral quadrant of the rostral brain stem.

It may be that the severity of axonal damage in the brain stem is of particular importance in determining the outcome. There were exceptions to this principle in the present series, i.e. cases with lesser grades of diffuse axonal injury who were vegetative or comatose, but it is possible that the relevant focal lesions were for some reason not identified.

In cases without diffuse axonal injury, it was more difficult to assess the relative contributions of the various types of lesion present. Thus, in every case with a secondary lesion in the brain stem, other lesions were present in the cerebral hemispheres or cerebellum, with wide variation in severity between cases. Hypoxic or ischaemic brain damage, for example, was present in all but one of these cases and ranged from infarction in arterial territories to boundary-zone ischaemic or diffuse hypoxic brain damage. In the absence of diffuse hypoxic or boundary-zone ischaemic damage, a macroscopic secondary brain-stem lesion appeared to be associated with a vegetative state or prolonged coma. The tegmentum of the midbrain was almost always involved, usually together with the pontine tegmentum. This is in keeping with non-traumatic brain-stem infarction causing disturbance of consciousness (Plum and Posner, 1980). The clinical significance of those lesions designated as microscopic secondary brain-stem lesions was more uncertain. None of the patients with this type of lesion was vegetative, and in each case there was also hypoxic/ischaemic damage or severe contusions which may have been responsible for severe disability. It is possible that these microscopic brain-

stem lesions were relatively unimportant.

Diffuse hypoxic or boundary-zone ischaemic damage tended to be associated with the vegetative state or prolonged coma. It is possible that the severe outcome in cases with boundary-zone ischaemic damage was partly related to diffuse involvement of the thalamus in most of these cases. In the absence of a macroscopic secondary brain-stem lesion, infarction within arterial territories or in the region of the basal ganglia was associated with severe disability. The purpose of including a possible example of the 'locked-in' syndrome was to draw attention to the very profound degree of disability that can result from very small but strategically-placed infarcts. In this patient, small bilateral infarcts involving the internal capsules produced a quasi-vegetative state. The findings in this case bore a superficial resemblance to diffuse axonal injury in that the brain was almost normal macroscopically, while on microscopic examination the most striking finding was bilateral symmetrical Wallerian degeneration in the pyramidal tracts. Without a careful neuropathological examination, the underlying infarcts could easily have been missed. Bilateral infarctions involving the internal capsules were found in 3 other cases in the series, but in all of these there were other lesions, such as a macroscopic brain-stem lesion or boundary-zone ischaemic damage with thalamic involvement, which also contributed to the clinical outcome.

In general, the outcome in each case could be related to the severity or extent of diffuse axonal injury, hypoxic/ischaemic

brain damage, or a secondary lesion in the brain stem. At first consideration, contusions appeared to be relatively unimportant, in keeping with their essentially focal and superficial nature in many of the cases. Analysis of the severity of contusions in relation to other types of lesion and outcome tended to substantiate this view, in that there was almost an inverse relation between severity of outcome and total contusion index. This was most marked in cases with diffuse axonal injury: the contusions in vegetative patients tended to be mild and considerably less severe than in those who were severely disabled. In cases with hypoxic/ischaemic damage and/or a secondary lesion in the brain stem, the median total contusion indices were similar in each outcome group. There were, however, three further cases in which there was the surprising finding that contusional damage was ostensibly the only lesion present to account for the clinical outcome. One of these was a vegetative patient with the highest equal contusion index recorded in the series, but these cases nevertheless seemed to be anomalous. It is possible that some other unidentified lesion in reality accounted for the clinical outcome, perhaps masked by the severity of the contusional damage. Diffuse axonal injury would be one possibility, although one of these cases had experienced a lucid interval.

When the lesions which appeared to contribute most to the outcome in each case were identified, diffuse axonal injury emerged as the most common (52% of cases), followed by hypoxic/ischaemic brain damage (23%), then hypoxic/ischaemic

brain damage together with a macroscopic secondary lesion in the brain stem (17%). Diffuse axonal injury was the most common cause of the vegetative state and was second to hypoxic/ischaemic damage, with or without a secondary lesion in the brain stem, as the cause of prolonged coma or severe disability. Grade 3 diffuse axonal injury, diffuse hypoxic and boundary-zone ischaemic damage together accounted for the great majority (86%) of cases of the vegetative state or prolonged coma. The relation between a lucid interval and the lesion contributing most to outcome was examined. This confirmed the absence of a lucid interval in cases with diffuse axonal injury, as in previous studies (Strich, 1956; Adams et al., 1982). In almost all the cases with a lucid interval, secondary lesions were confirmed to be present.

The development of an intracranial haematoma is of major significance clinically since this may precipitate a rise in intracranial pressure with secondary damage to the brain stem. The cases in the present series were divided into two groups according to whether or not a haematoma had been evacuated, and then analysed with respect to the main lesions present. This showed that in patients in whom a haematoma had been evacuated, secondary lesions were the most common cause of a poor outcome, although diffuse axonal injury was present in almost a quarter of these cases. Adams et al. (1982), however, found intracranial haematomas (large enough to act as space-occupying lesions) in 11% of their series of cases with diffuse axonal injury. In those cases without evacuation of a haematoma,

diffuse axonal injury was by far the most common lesion in the present series, although in a small number of these secondary lesions were also present.

Hydrocephalus is known to be common after head injury, particularly in patients of longer survival. Jellinger and Seitelberger (1970) found hydrocephalus in 50% of their series of post-traumatic encephalopathy. In the present series it was deemed to be present in 65% of those cases analysed, based on an arbitrary upper limit of normal for the ventricle/brain ratio in a single brain slice of 5.5%, a value which compares with those of 5% in a post-mortem study (Hubbard and Anderson, 1981) and 7.7% in an ante-mortem radiological study (Meyers et al., 1983), bearing in mind that the ventricles are known to decrease in size after death (Sarwar and McCormick, 1978). Strich (1956) in her cases of diffuse degeneration of the cerebral white matter attributed hydrocephalus to loss of white matter. Following this up, Meyers et al. (1983) distinguished radiologically between early and late ventricular enlargement according to whether this occurred before or after 30 days. Neuropsychological test performance was found to be related to ventricular size only when enlargement was delayed, and it was postulated that delayed hydrocephalus is due to diffuse axonal injury and hypoxic/ischaemic damage. In the present series, the degree of hydrocephalus tended to increase with time in cases both with diffuse lesions and with focal lesions only. The correlation with duration of survival was strongest for patients in a vegetative state due to diffuse axonal injury. The two

most severe examples of hydrocephalus in the present series were in cases of long survival respectively with diffuse hypoxic brain damage and diffuse axonal injury. An origin ex vacuo was most likely in these and was probably relevant in most of the remaining cases. Although no definite cause of obstruction was found, it is difficult to exclude the possibility of compensated obstructive hydrocephalus. In general, the present study shed little light on the precise mechanisms of hydrocephalus.

Hydrocephalus, whether ex vacuo or obstructive in type, is a complication of head injury which bears a more or less direct relationship to brain damage received at the time of injury or its immediate aftermath. In vegetative or severely disabled patients, other complications may arise which are unrelated to the original injury. There were three such cases in the present series. One of these had clinical and pathological features of cerebro-vascular disease which contributed to severe disability. The other two cases were examples of rare diseases of nutritional or metabolic origin, presumably consequences of the debilitated states of these patients. As a sporadic disease, pellagra is virtually confined to malnourished alcoholics, and a search of the literature has failed to identify any previous case either in a post-traumatic patient or as a complication of long-term artificial nutrition. In the case described here, any relation with alcohol can be ruled out. It is likely that deficiency of niacin derived from the substances used for tube feeding. The other case of interest in this context was one in

which the features of central pontine myelinolysis and Marchiafava-Bignami disease were combined. Central pontine myelinolysis is another disease which tends to be associated with alcohol abuse (Goebel and Herman-Ben Zur, 1975), although recently the role of fluid and electrolyte disturbances has been emphasised both clinically (Cambier et al. 1977; Oda et al., 1984) and experimentally (Laureno, 1983). A few post-traumatic cases of central pontine myelinolysis have been described, not only in the acute phase (Seitelberger and Jonasch, 1970), but also in patients of long survival with electrolyte disturbances, including a vegetative child (Minauf and Jellinger, 1970) and two quadriplegic adults (Kalnins et al., 1984). Marchiafava-Bignami disease, on the other hand, appears to be virtually exclusive to alcoholics (Brion, 1975). A combination of central pontine myelinolysis and Marchiafava-Bignami disease has been described in only 4 cases (Tariska, 1967; Sherins and Verity, 1968; Ghatak et al., 1978; Regadera et al., 1983). All these patients, however, were alcoholics with no history of trauma. Previous alcohol consumption may have been relevant in the case described in the present study, but access to alcohol during the three year period of severe disability seems highly unlikely. An alternative explanation may be that lesions in the corpus callosum form part of a spectrum of central pontine myelinolysis associated with multiple demyelinating lesions in the cerebral hemispheres (Kalnins et al., 1984; Cambier et al., 1977; Finlayson et al., 1973; Oda et al., 1984).

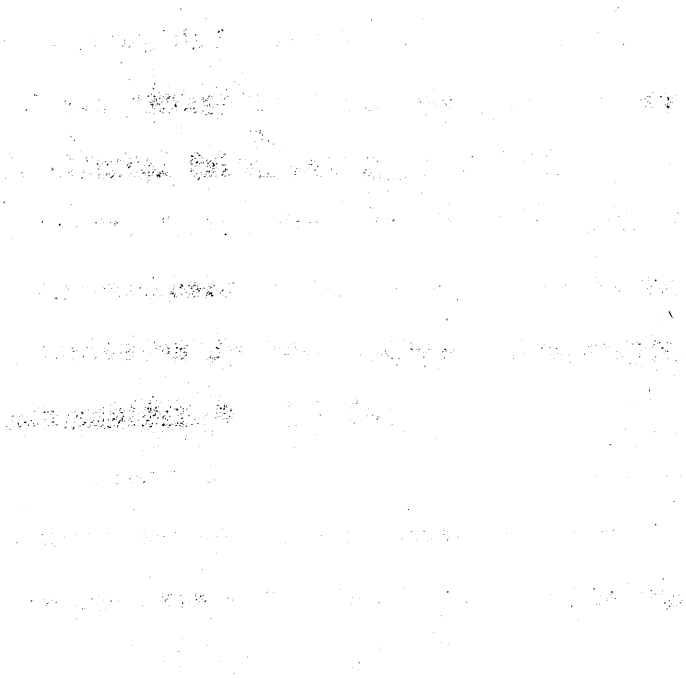
Perhaps the most important finding of the present study is

that diffuse axonal injury was the cause of the vegetative state or severe disability in over half the cases in the series, and greatly outnumbered the other principal causes of poor outcome, namely hypoxic/ischaemic brain damage and secondary lesions in the brain stem. How does this series compare with other surveys of brain damage after head injury, notably those of Jellinger and Seitelberger (1970) and Adams et al. (1980a)? It might be argued that all these studies are similar in that they are based on patients who were comatose after a severe head injury and died prematurely, in some cases after "recovery" to a vegetative state or severe disability. The most important difference between the three series is probably the duration of survival of the patients. The relative numbers of patients respectively in coma, a vegetative state or severe disability must depend to some extent on the length of survival. The present series and that of Jellinger and Seitelberger (1970) are small, allowing potential for chance variation in the proportion of various types of brain damage. Allowing, however, for major differences in interpretation, it is likely that diffuse axonal injury was the most common cause of protracted post-traumatic encephalopathy in the series of Jellinger and Seitelberger (1970). What has come to light are the substantial differences between the present series of patients living longer than a month and that of Adams et al. (1980a), the majority of whose cases lived for less than one month. Specifically, Adams et al. (1980a) found a much lower incidence of diffuse axonal injury, amounting to only 13% of cases. Since the incidence and types

of hypoxic/ischaemic brain damage are broadly similar between the present series and that of Adams et al. (1980a) (with the exception of infarction in the basal ganglia), the implication is that a high proportion of deaths in the series of Adams et al. (1980a) were due to complications of the original injury leading to secondary lesions in the brain stem. The high incidence of infarction in the basal ganglia and thalamus (Graham, Adams and Doyle, 1978) is in keeping with this suggestion. It would appear that secondary lesions in the brain stem, in contrast with diffuse axonal injury, tend not to be compatible with long survival. Any series of patients surviving the acute period after a head injury is thus likely to contain a relatively high proportion of cases with diffuse axonal injury.

Since diffuse axonal injury is such a common cause of the vegetative state and severe disability after head injury, it is likely to be a common cause of less severe post-traumatic disability. Mild diffuse axonal injury (i.e. grade 1, as in the present study) was identified by Pilz (1983a) in 11% of an unselected series of fatal head injuries. Graham et al. (1989) identified a group of patients who experienced a complete lucid interval, and were therefore considered to have sustained mild head injuries although they subsequently died as a result of complications such as intracranial haematomas. Grade 1 diffuse axonal injury was present in only 3% of these cases. The implication of the work of Oppenheimer (1968) and Clark (1974) on microglial clusters is that mild diffuse axonal injury is more common than these studies of Pilz (1983a) and Graham et al.

(1989) suggest. Research on mild head injury in experimental animals has now identified minor axonal changes short of retraction ball formation, including degeneration and apparent fragmentation of axons (Gennarelli et al., 1983) and axonal swelling (Povlishock et al., 1983). It should be possible to identify corresponding changes in humans. What is required is a detailed and systematic autopsy study of patients with mild head injury, with a view to identifying and assessing the severity of diffuse axonal injury, particularly at the milder end of the spectrum, at different stages of survival. One day it may be possible to show that the basis of the well recognised minor neuropsychological sequelae after head injury (Symonds, 1962; Barth et al. 1983) is diffuse axonal injury.



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ILLUSTRATIONS

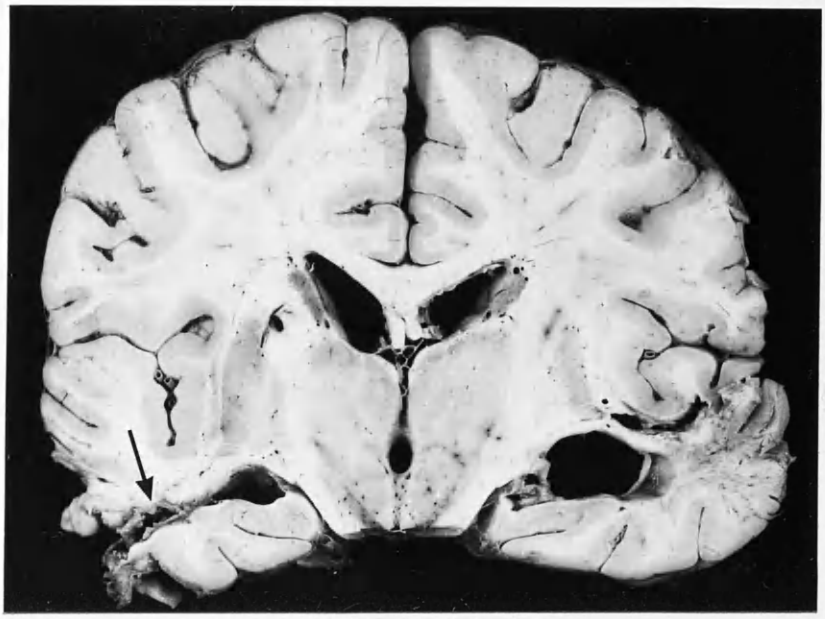


Fig. 5.1 Case 16. Severely disabled, survival 54 days. Bilateral extensive temporal contusions. On left side these involve deep white matter (depth grade 4) and lateral and inferior surfaces of the lobe (extent grade 3), hence contusion index of 12 for this locator. Bilateral temporal haematomas were evacuated neurosurgically. Small abscess (arrowed) is seen beside left temporal horn. There is residual mild ventricular dilatation after treatment of obstructive hydrocephalus.

Fig. 5.2 Case 19. Severely disabled, survival 59 days. Residual left temporal haematoma after evacuation of burst left temporal lobe. There is a persistent supracallosal hernia on left side. Moderate asymmetrical hydrocephalus also present.

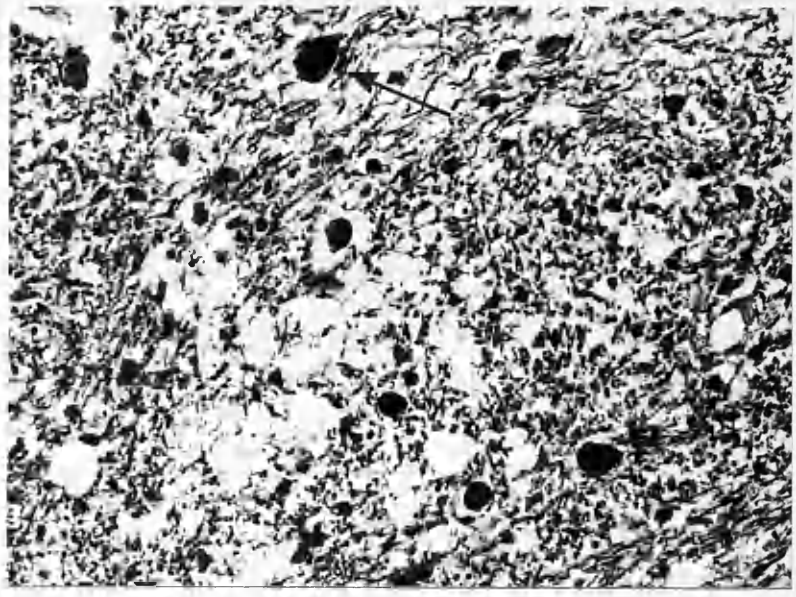


Fig. 6.1 Case 20. Vegetative, survival 59 days. Diffuse axonal injury: retraction balls (arrow) in basis pontis. Coarse vacuolation of neuropil is a characteristic feature. Palmgren, x 250.

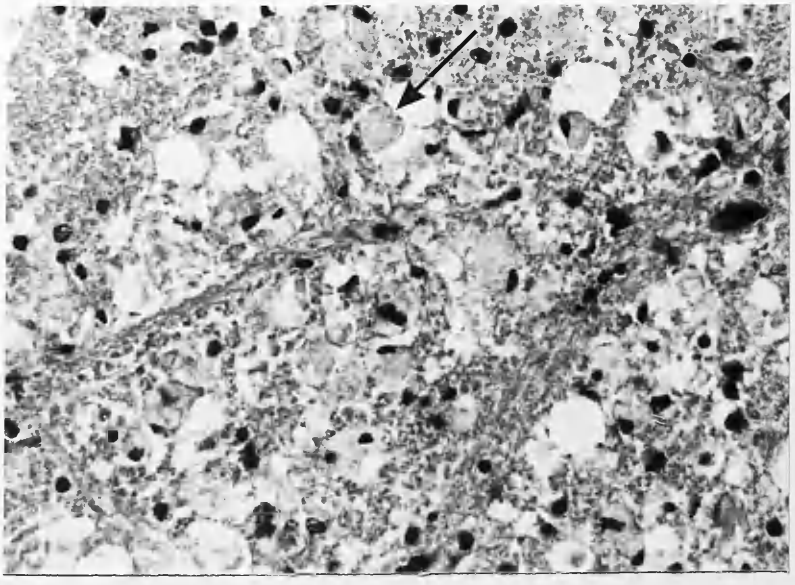


Fig. 6.2 Same case as Fig. 6.1. Long-tract degeneration indicated by presence of lipid-laden phagocytes (arrow) in descending tracts of basis pontis. Haematoxylin and eosin, x 250.

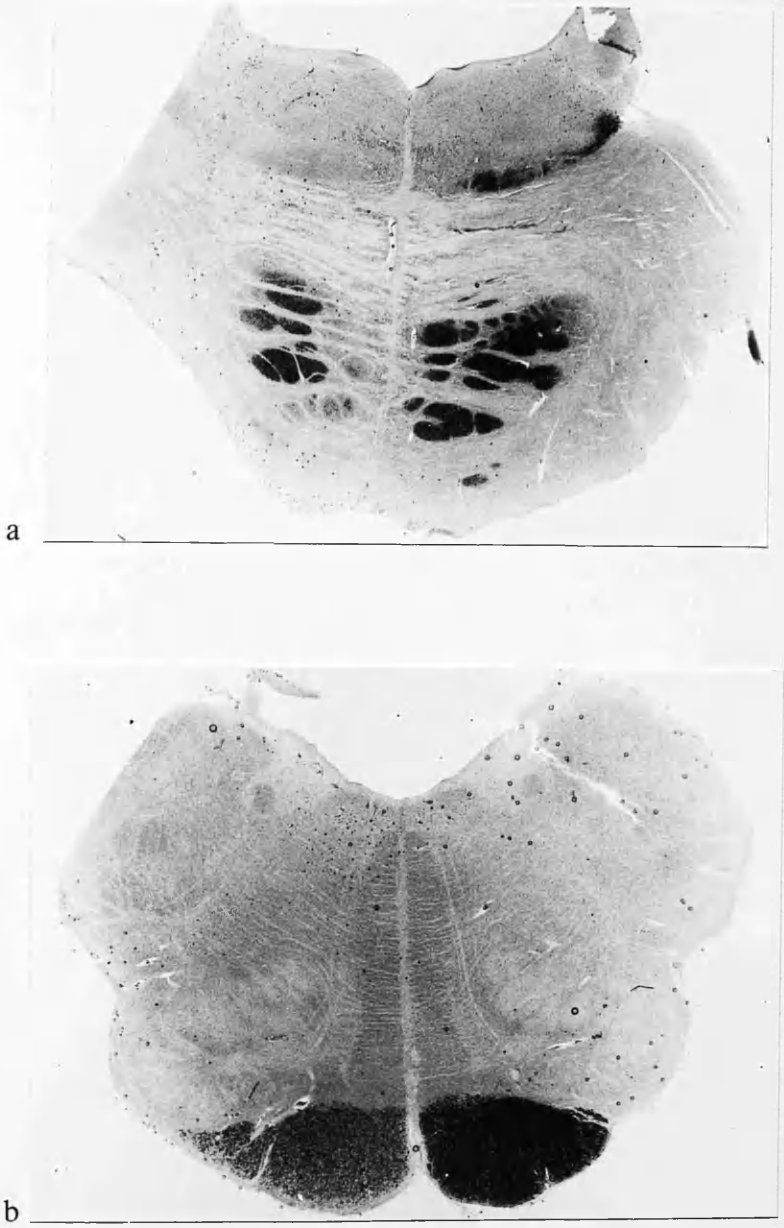


Fig. 6.3 Case 34. Severely disabled, survival 157 days. Diffuse axonal injury: Wallerian degeneration of myelin (stained black). There is asymmetrical involvement of long tracts in the pons (a), and the medulla (b). Marchi.

Fig. 6.4 Case 44. Vegetative, survival six years. Diffuse axonal injury: demyelination demonstrated by pallor of staining, predominantly parasagittal. Celloidin section, Woelcke.

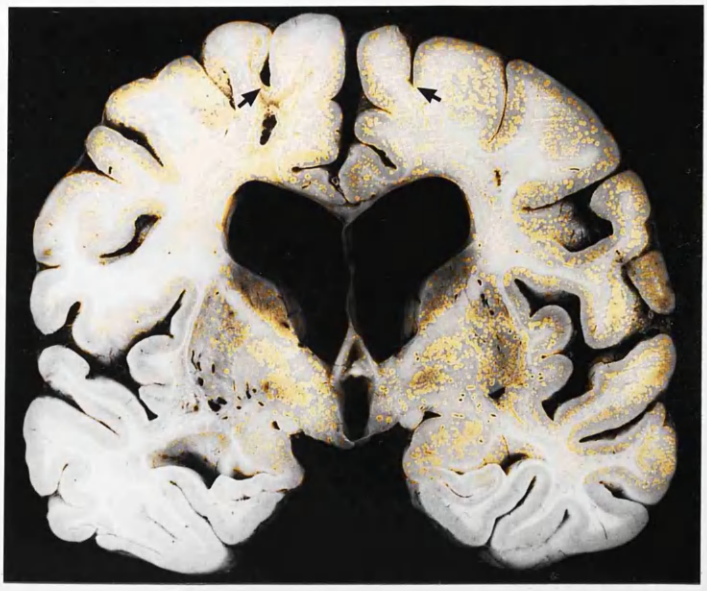


Fig. 6.5 Same case as Fig. 6.4. Diffuse axonal injury: demyelination apparent to naked eye as shrunken greyish tissue at dorsal paramedian regions of cerebral hemispheres. Sulcal infarcts are present (arrows). Cerebral atrophy is indicated by widening of sulci and moderately severe hydrocephalus.

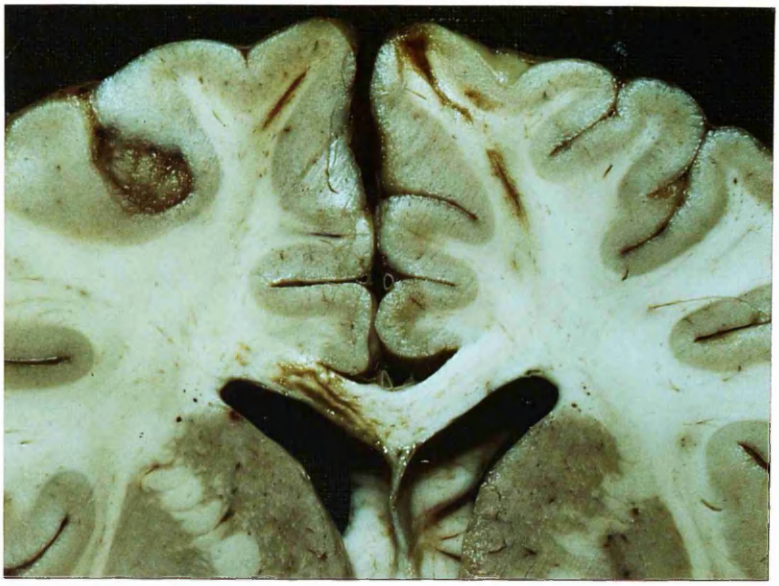


Fig. 6.6 Case 27. Vegetative, survival 86 days. Diffuse axonal injury: pigmented cystic focal lesion in corpus callosum. Similarly pigmented streaks in dorsal paramedian areas of cerebral hemispheres are gliding contusions.

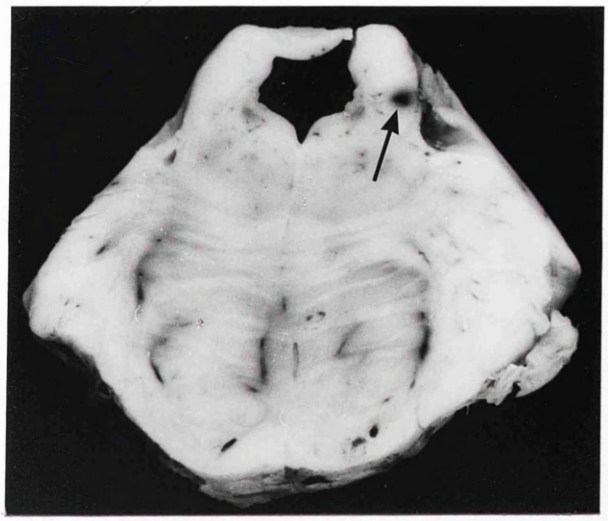
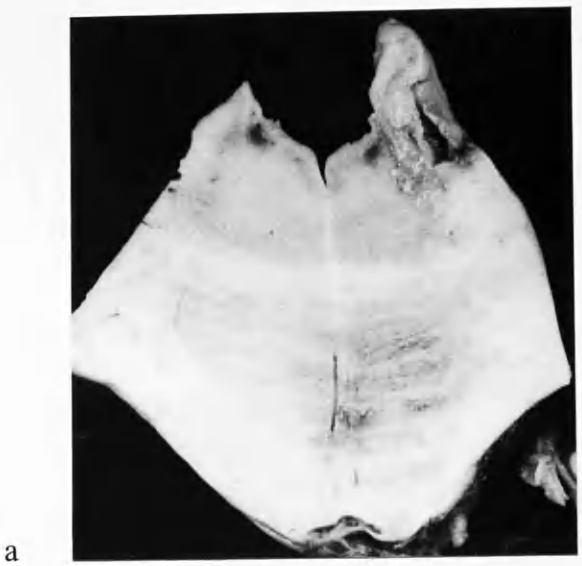


Fig. 6.7 Case 9. Vegetative, survival 38 days. Diffuse axonal injury: focal haemorrhagic lesion in superior cerebellar peduncle (arrow).



a

b

Fig. 6.8 Case 46. Vegetative, survival 8 years 6 months. Diffuse axonal injury: cystic focal lesion in superior cerebellar peduncle seen macroscopically (a), and microscopically (b). (b) Phosphotungstic acid haematoxylin, x 25.

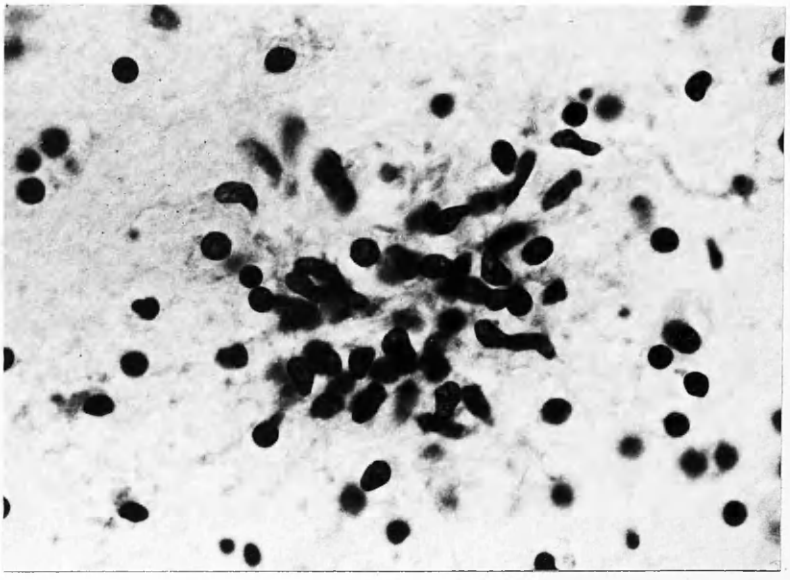


Fig. 6.9 Case 29. Vegetative, survival 95 days. Diffuse axonal injury: microglial cluster. 20μ paraffin section, cresyl violet, x 400.

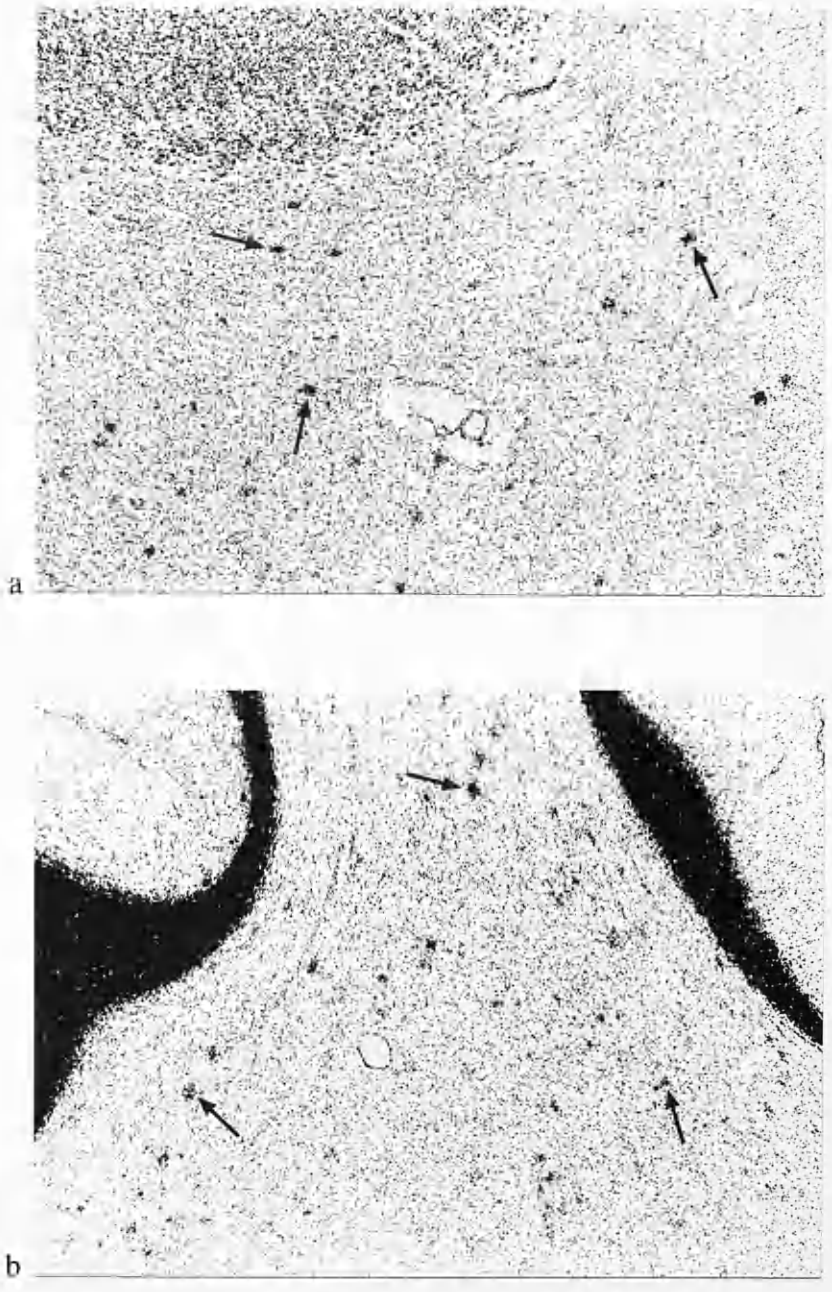


Fig. 6.10 Case 13. Vegetative, survival 43 days. Diffuse axonal injury: numerous microglial clusters (arrows) in white matter of occipital lobe (a) and cerebellum (b). Celloidin section, Nissl x 40.

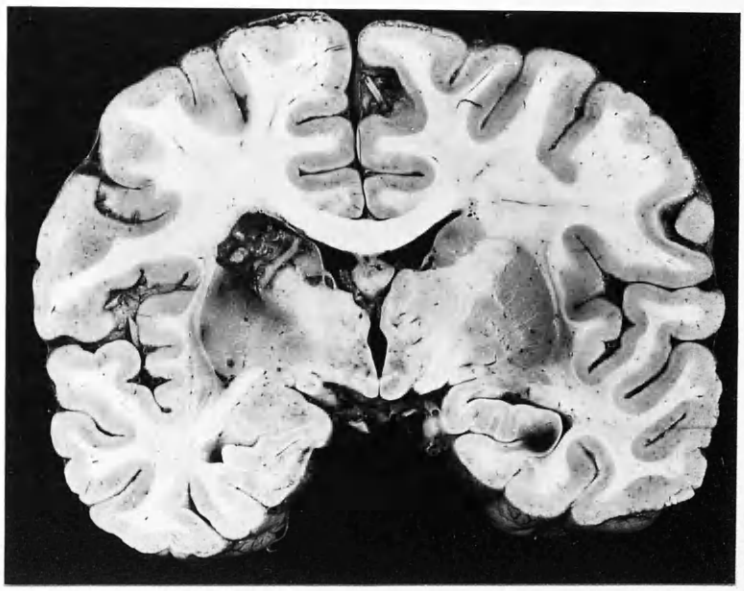
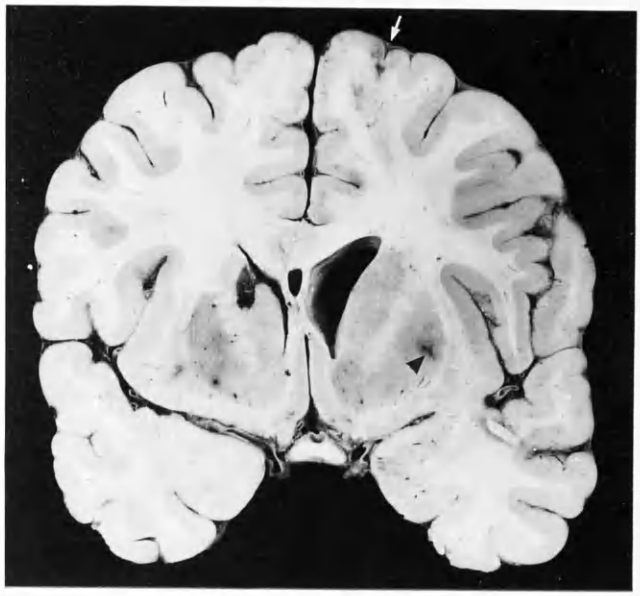


Fig. 6.11 Case 3. Vegetative, survival 30 days. Diffuse axonal injury/diffuse vascular injury. Pigmented cystic infarct on left side involving head of caudate nucleus and internal capsule. There is a minute haematoma in the right pes hippocampi. (See also Fig. 6.15).



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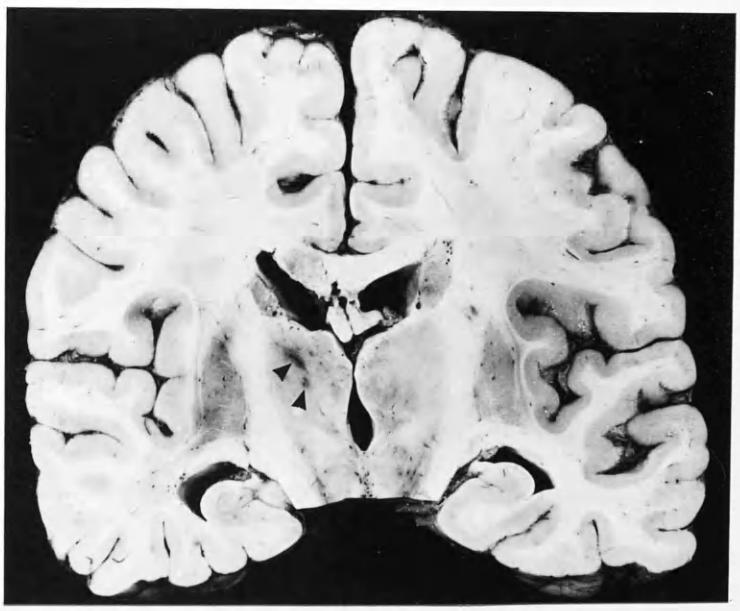

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Fig. 6.12 Case 13. Vegetative, survival 43 days. Diffuse axonal injury/diffuse vascular injury. Focal lesion in corpus callosum extended over whole length of corpus callosum. Vascular lesions include sulcal infarct and adjacent gliding contusion (arrow) (a) and scattered minute lesions (arrowheads) in corpus striatum and thalamus (a and b). Small haematoma in head of left caudate nucleus may be related to intraventricular cannulation.

Fig. 6.13 Case 13. Vegetative, survival 43 days. Diffuse axonal injury: sulcal infarct. Celloidin section, Nissl, x 40.

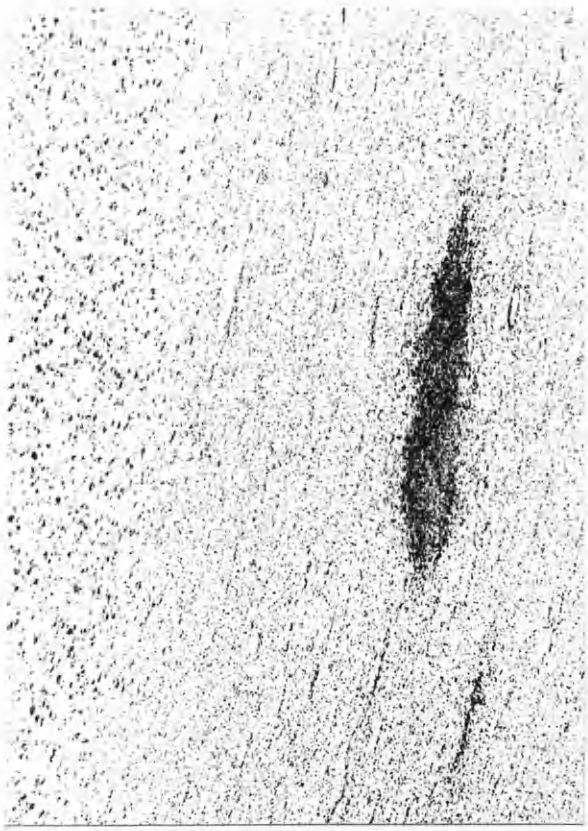


Fig. 6.14 Case 13. Vegetative, survival 43 days. Diffuse axonal injury: gliding contusion in superior frontal gyrus represented by linear zone of haemosiderin-laden macrophages. There is intense gliosis in the surrounding parenchyma. Celloidin section, Nissl, x 40.

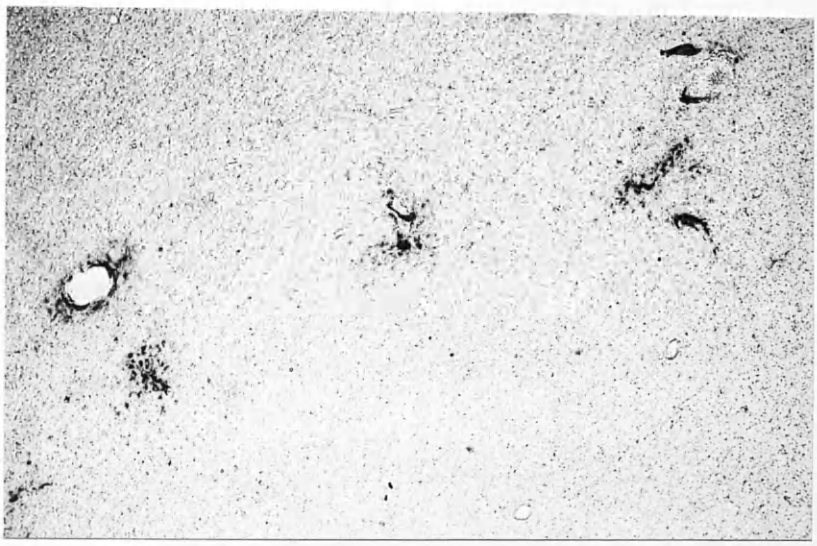


Fig. 6.15 Case 3. Vegetative, survival 30 days. Diffuse vascular injury: multiple vascular lesions in white matter of temporal lobe as revealed by perivascular deposits of haemosiderin. Celloidin section, Perls, x 40.

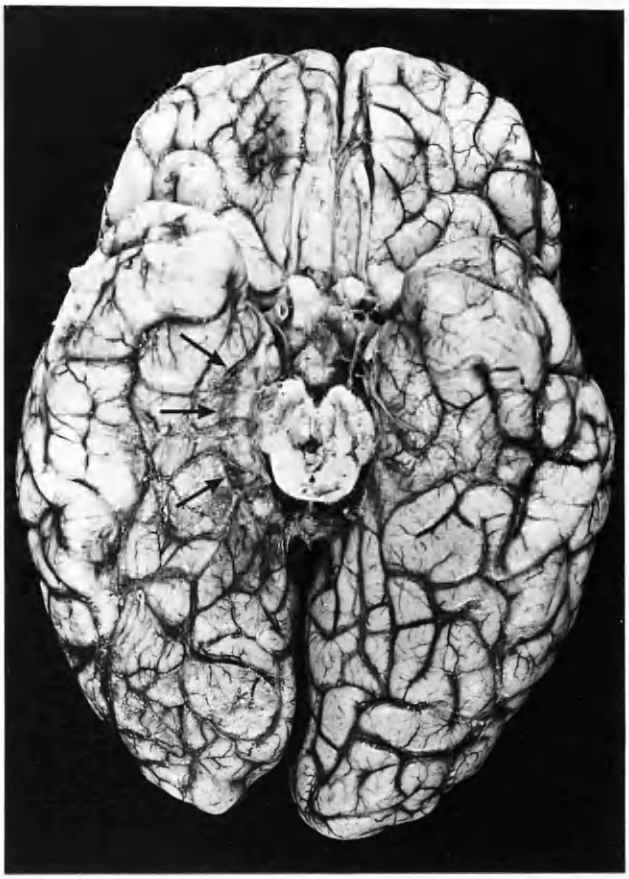


Fig. 7.1 Case 18. Vegetative, survival 57 days. Previous tentorial herniation marked by linear zone of pressure necrosis (arrows). Secondary infarction in brain stem also seen (shown better in Fig. 7.3).

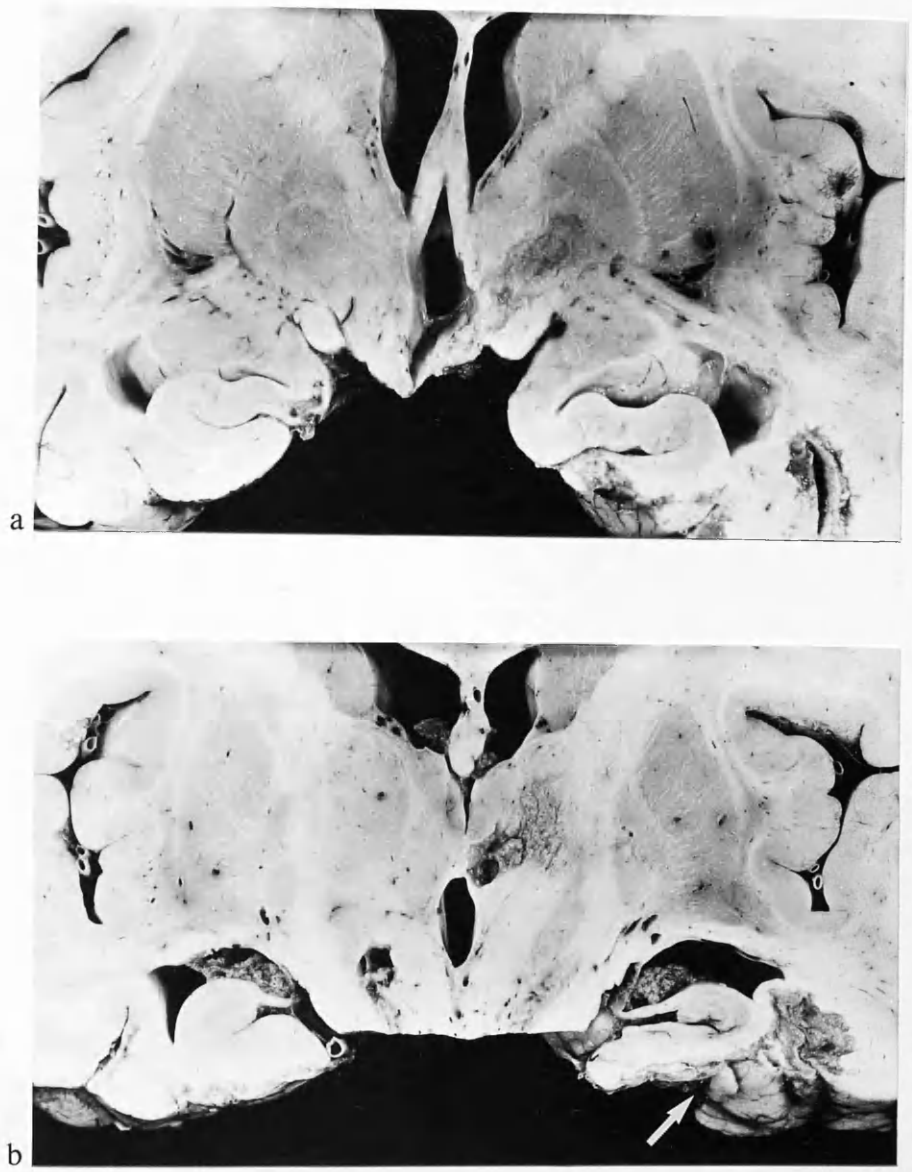


Fig. 7.2 (Same case as Fig. 7.1). Infarction secondary to raised intracranial pressure. This involves globus pallidus and hypothalamus on right side (a), and right thalamus, left subthalamic region and territories of both posterior cerebral arteries (b). Groove formed by tentorial herniation is also shown (arrow).

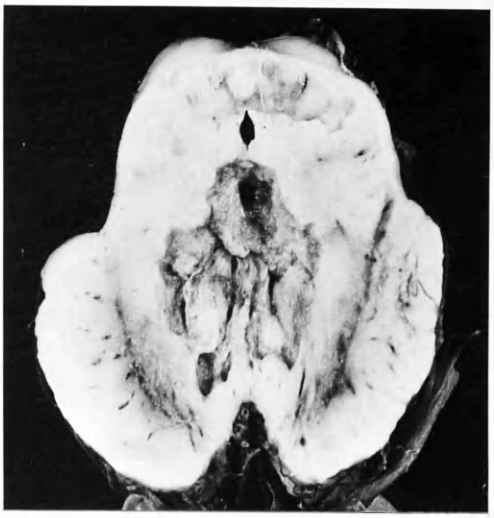
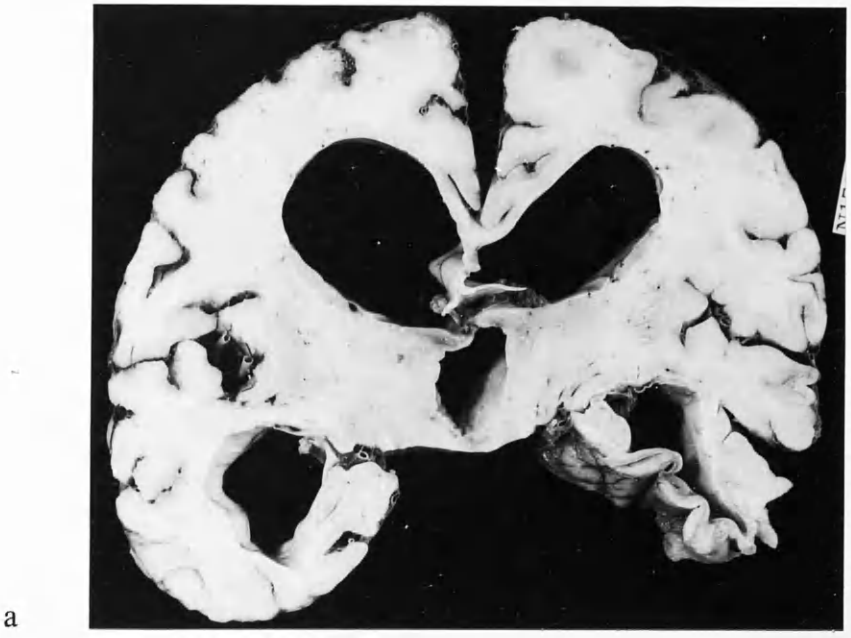


Fig. 7.3 (Same case as Figs. 7.1 and 7.2). Cystic infarction in tegmentum of mid-brain, secondary to raised intracranial pressure.

Fig. 7.4 Case 14. Severely disabled, survival 47 days. Previous tentorial herniation indicated by wedge of pressure necrosis seen histologically. Celloidin section, Nissl.

Fig. 7.5 Case 6. Prolonged coma, survival 34 days. Haematoma in pons secondary to raised intracranial pressure.

Fig. 7.6 Case 5. Prolonged coma, survival 33 days. Infarction in brain stem secondary to raised intracranial pressure. Lesions seen in tegmentum of mid-brain and cerebral peduncle. The latter is an example of the Kernohan notch. Celloidin section, myelin.



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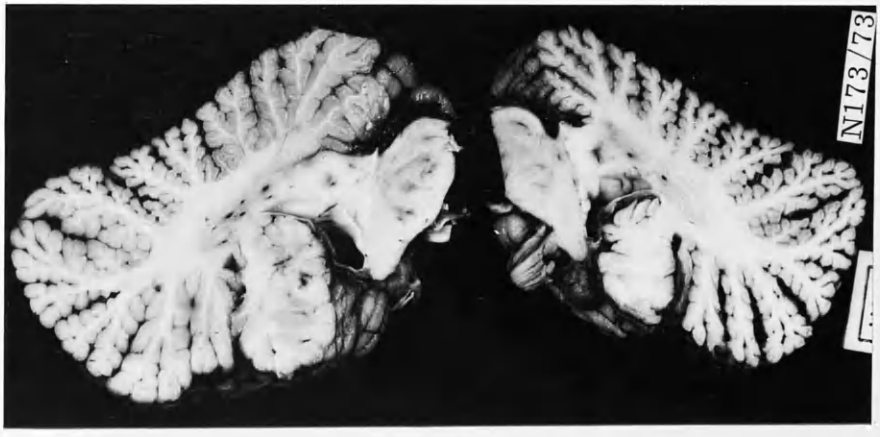


b

Fig. 8.1 Case 42. Vegetative, survival 3 years. Diffuse hypoxic brain damage. There is severe hydrocephalus associated with marked atrophy of the cerebral hemispheres (a) and cerebellum (b).

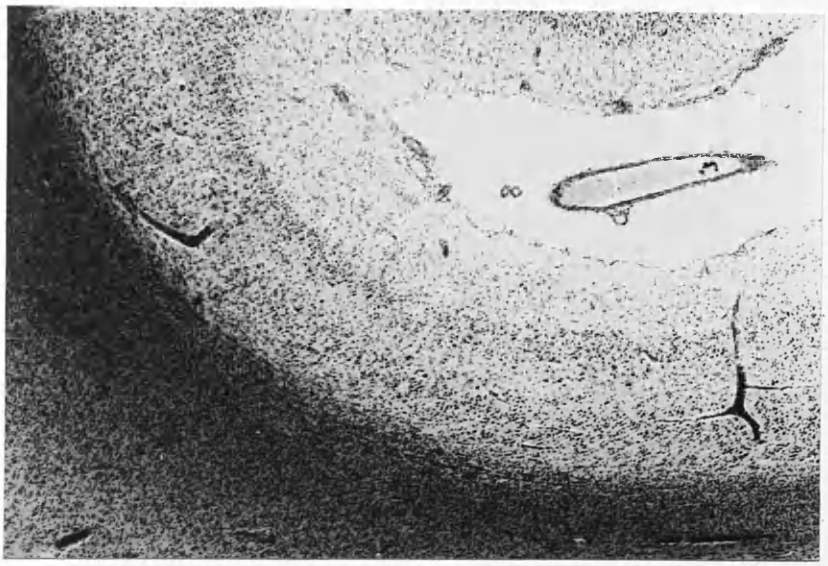


Fig. 8.2 (Same case as Fig. 8.1). Diffuse hypoxic brain damage. Extensive neuronal loss of laminar distribution, with reactive gliosis. 20μ paraffin section, cresyl violet, x 40.

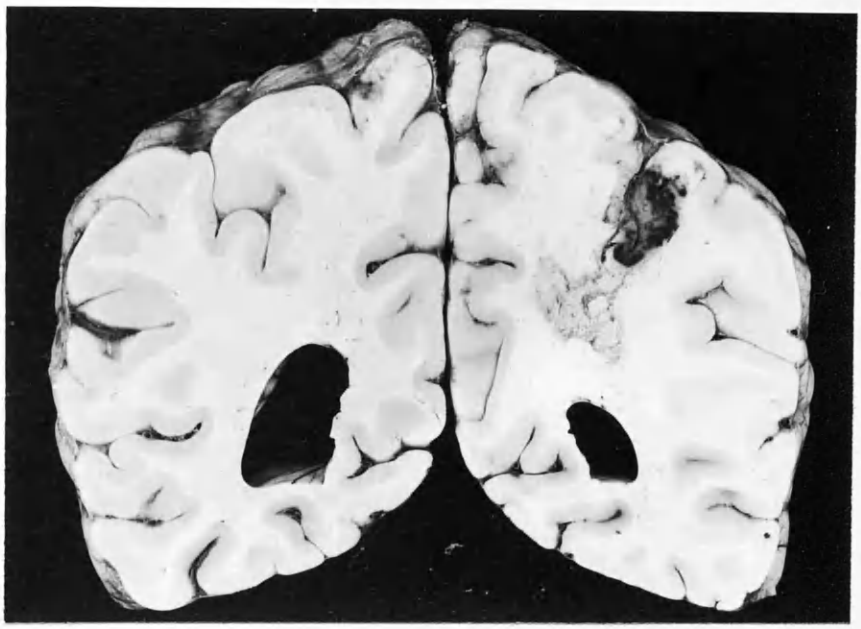


Fig. 8.3 Case 4. Prolonged coma, survival 30 days. Infarction in boundary zone between cerebral arterial territories.

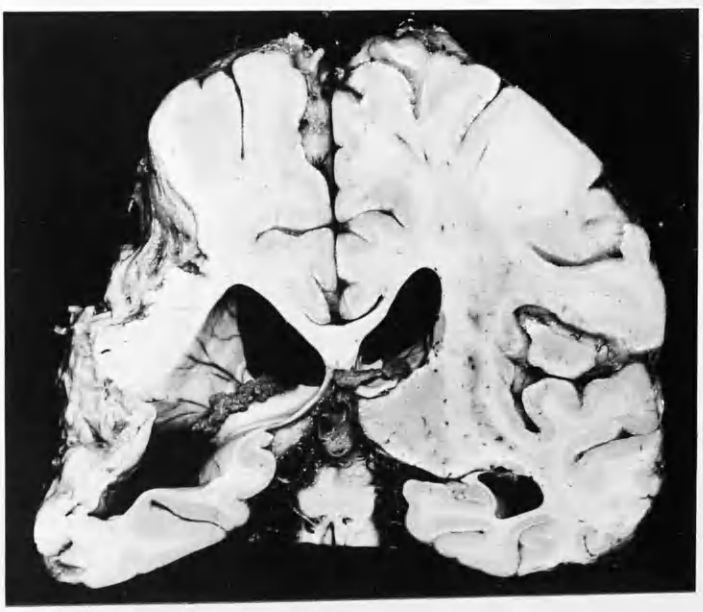
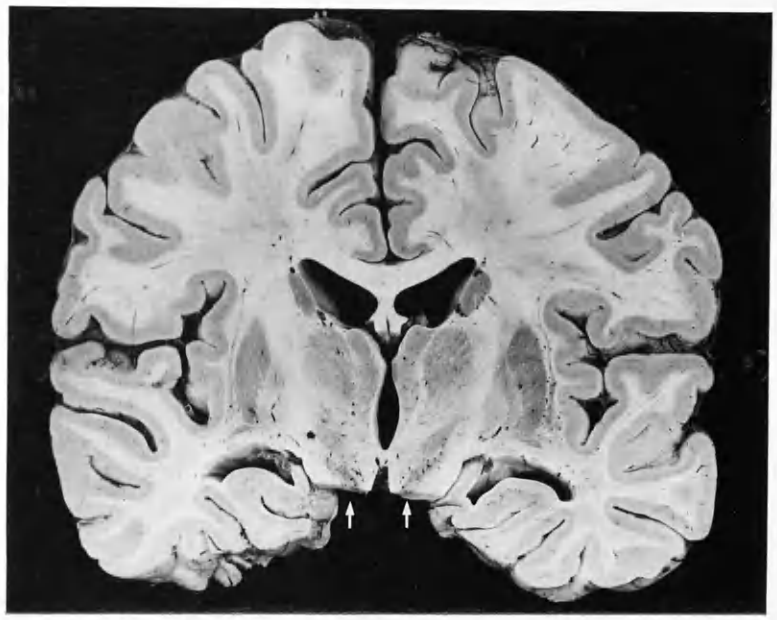


Fig. 8.4 Case 31. Severely disabled, survival 129 days. Infarction in territory of left middle cerebral artery.

Fig. 8.5. Case 17. Severely disabled, survival 56 days. Bilateral infarcts involving internal capsules.

Fig. 8.6 Case 32. Severely disabled, survival 140 days. Abscess in left frontal lobe.



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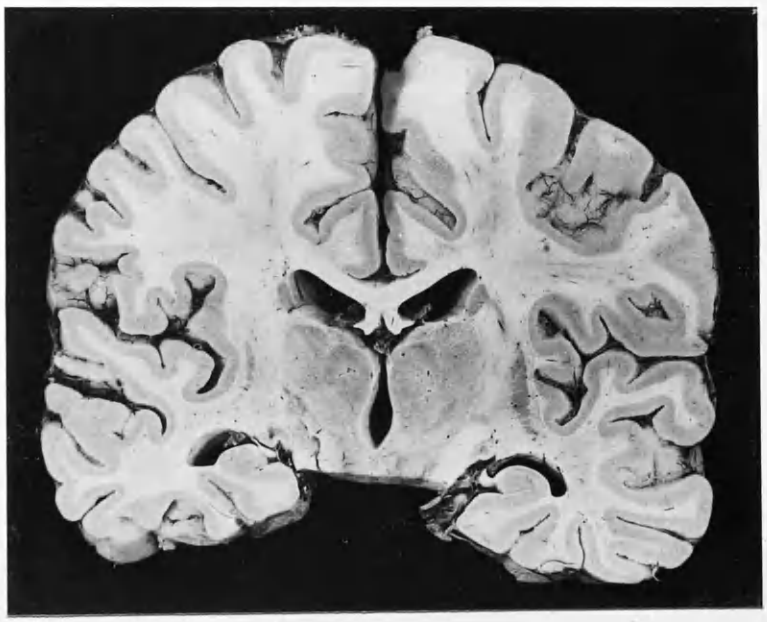
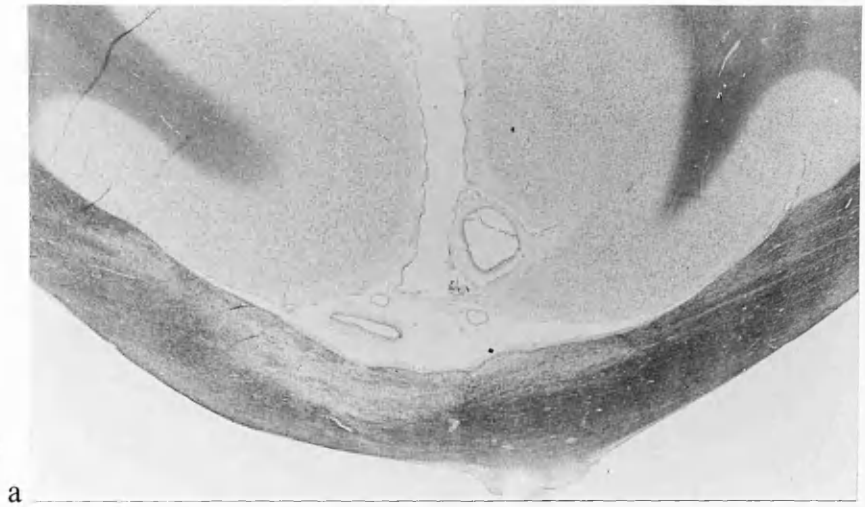


b

Fig. 9.2 Case 33. Severely disabled (possible "locked-in" syndrome), survival 147 days. Infarcts secondary to a high intracranial pressure, including bilateral small lesions (arrows) in the substantia nigra (a) and a larger lesion mainly involving the left internal capsule (b).



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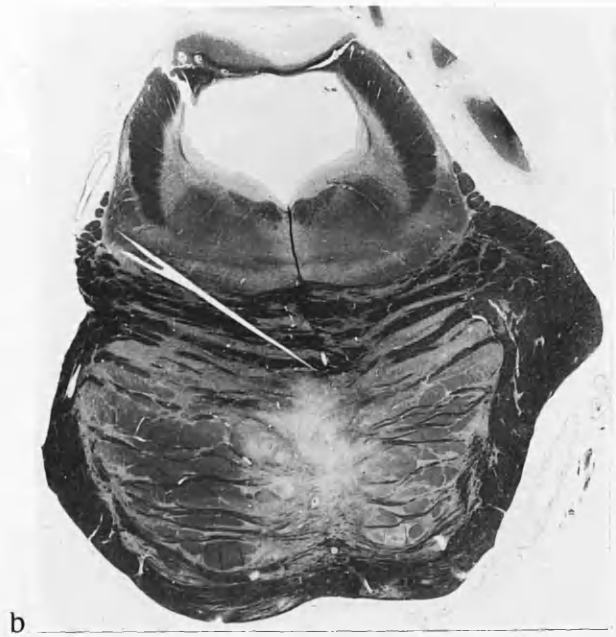
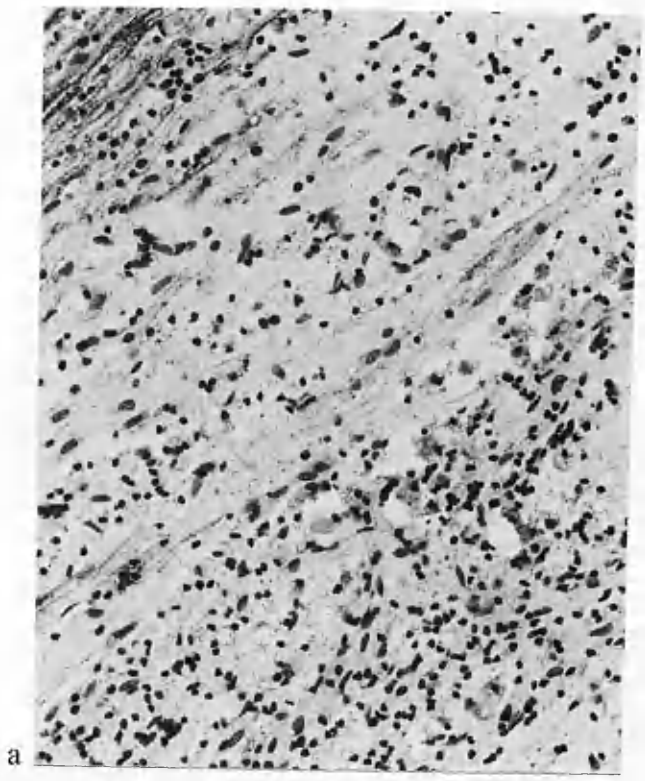


b

Fig. 10.2 Case 43. Severely disabled, survival 3 years and 2 months. Marchiafava-Bignami disease and central pontine myelinolysis. Central zones of demyelination are present in the corpus callosum (Marchiafava-Bignami disease) (a), and in the basis pontis (central pontine myelinolysis) (b). Luxol fast blue/ cresyl violet.



a

b

Fig. 10.3 (Same case as Fig. 10.2). Marchiafava-Bignami disease. The lesion in the corpus callosum is infiltrated by macrophages and glial cells (a). Axons are present within the lesion (b). a : Luxol fast blue/cresyl violet, x 250; b : Palmgren, x 100.

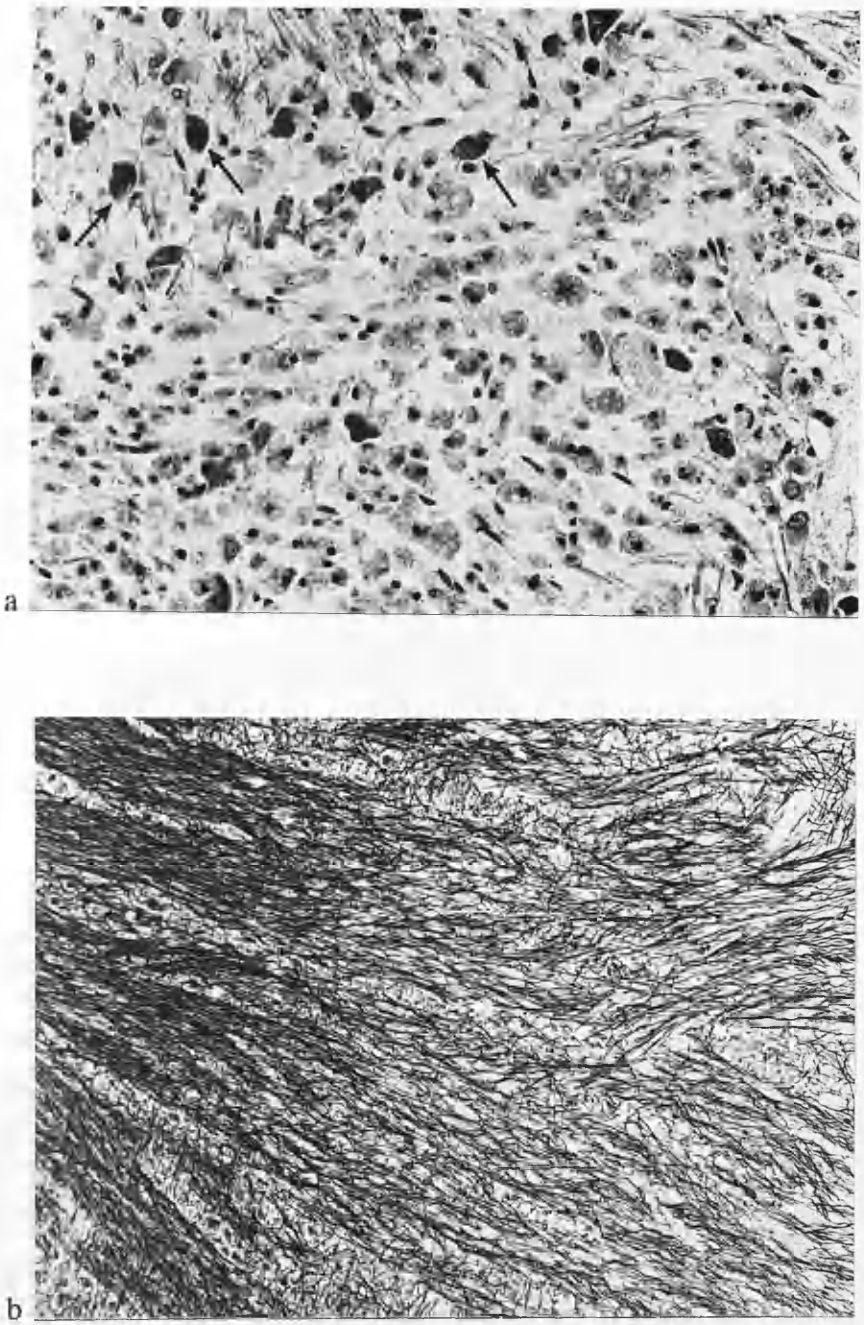
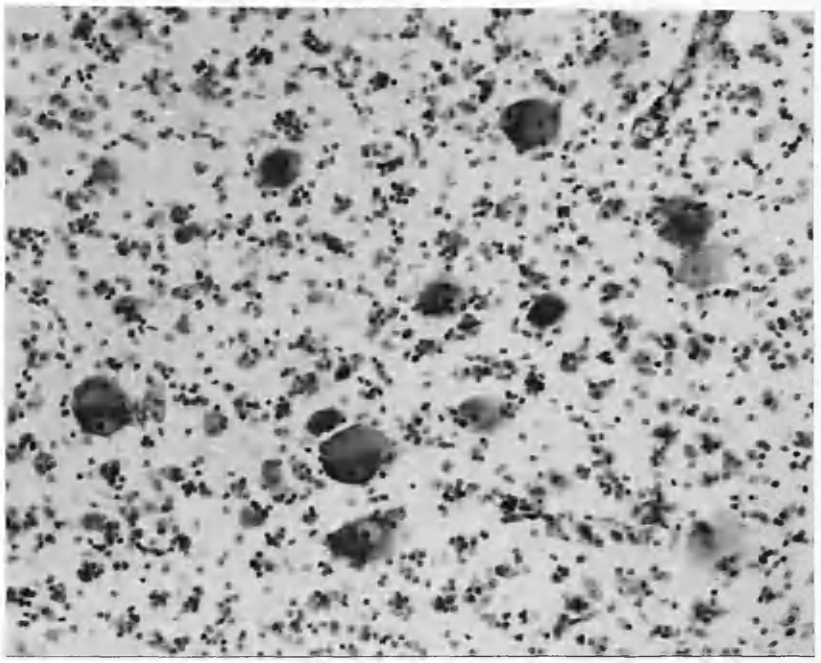
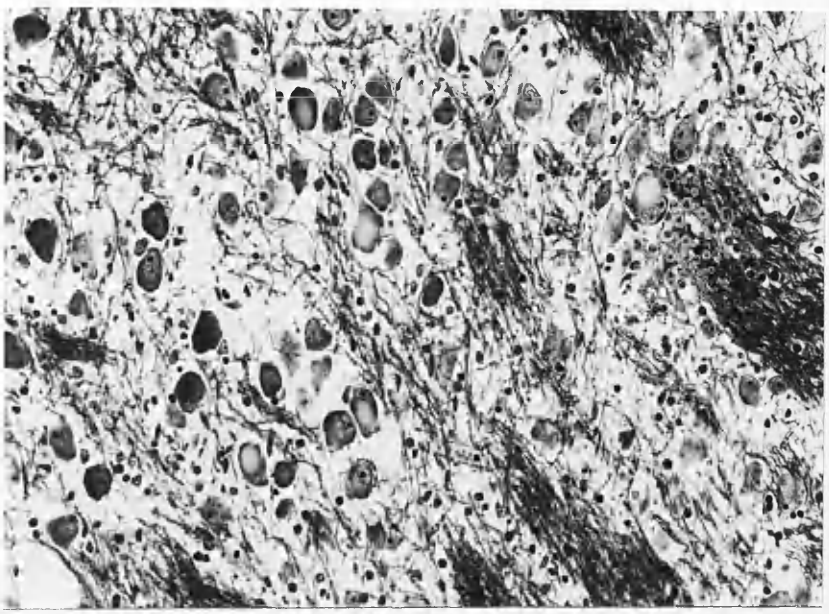


Fig. 10.4 (Same case as Figs. 10.2 and 3). Central pontine myelinolysis. The lesion in the basis pontis is infiltrated by macrophages and glial cells (a). Neurons are spared (arrows). There is preservation of axons (b) within the lesion (the paler area to the right of the photograph). a : Luxol fast blue/cresyl violet, x 250; b : Palmgren, x 100.



a



b

Fig. 10.5 Case 44. Vegetative, survival 6 years. Pellagra. Central chromatolysis is shown by ballooning of neuronal perikarya, with central loss of Nissl substance, affecting Betz cells of the motor cortex (a) and the nuclei of the basis pontis (b). a : Celloidin section, Nissl, x 100; b : Luxol fast blue/cresyl violet, x 250.