Pathology of hypoxic brain damage in man

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The energy requirements of the brain demand amongst other things adequate supplies of oxygen and glucose. These are provided by the functions of respiration and circulation. Neurons are particularly susceptible to hypoxia since they have an obligative, aerobic, glycolytic metabolism. The adult brain receives about 15 per cent of the cardiac output, or as expressed in terms of blood flow, about 45 ml/100 g/minute in the adult and about twice as much in children (McIlwain, 1966). The respiratory quotient of the brain is almost unity and glucose is the principal source of energy by oxygenation. If the supply of oxygen or glucose is reduced below a critical level consciousness is lost after a few seconds and irreversible brain damage may occur if the 'hypoxia' is more prolonged.

Physiology

The supply of oxygen to the brain depends on the cerebral blood flow (CBF) and the oxygen content of the blood. Cerebral blood flow in turn depends on the cerebral perfusion pressure (CPP) which is defined as the difference between the mean systemic arterial pressure (SAP) and the cerebral venous blood pressure. Blood flow to the brain shows a remarkable capacity for remaining constant, only hypercapnia, hypoxia and extreme hypotension affecting it to any marked extent. The preservation of CBF in response to changes in arterial blood pressure is brought about by autoregulation which can be defined as the 'maintenance of a relatively constant blood flow in the face of changes in perfusion pressure' (Harper, 1972). The mechanism of this autoregulation is still uncertain but it appears to be lost or at least severely impaired in a wide range of acute conditions producing brain damage (Bruce et al, 1973; Harper et al, 1975). Thus there are many situations in which cerebral autoregulation may be impaired before an episode of hypoxia. The level of CPP at which brain damage is produced is not known in man but in the presence of normal autoregulation the critical level of SAP is about 50 mm Hg (Harper, 1972). In primates with a normal PaO2, it would appear that brain damage does not occur until the CPP falls to less than 25 mm Hg (Brierley et al, 1969).

The energy state of the brain may also be severely reduced in the presence of normal supplies of oxygen and glucose by substances which poison the oxidative enzymes of nerve cells. These considerations form the basis of the various categories of brain hypoxia (Brierley, 1976; Adams, 1976).

Categories of brain hypoxia

1 STAGNANT
(a) Ischaemic is due to local or generalized arrest of blood supply; (b) oligaemic is due to local or generalized reduction in blood supply.

2 ANOXIC AND HYPOXIC
(a) Anoxic, an absence of oxygen in the lungs which leads to tissue anoxia; (b) hypoxic, a reduced oxygen tension in the lungs which leads to tissue hypoxia.

3 ANAEMIC
Anaemic is where there is insufficient haemoglobin in the blood to carry the oxygen in chemical combination.

4 HISTOTOXIC
Histotoxic is due to poisoning of neuronal respiratory enzymes.

5 HYPOGLYCAEMIC
Hypoglycaemic is due to a deficiency of the substrate glucose.

6 FEBRILE CONVULSIONS AND STATUS EPILEPTICUS

Hypoxic brain damage

Hypoxic brain damage may occur in any situation where there is an inadequate supply of oxygen or glucose to nerve cells. It is therefore a potential hazard to any patient subjected to general anaesthesia, a severe episode of hypotension, cardiac arrest, status epilepticus, carbon monoxide or...
barbiturate intoxication and hypoglycaemic coma. The eventual degree of clinical recovery will be determined by whether or not satisfactory resuscitation can be achieved before permanent brain damage ensues. Crises of this kind are not uncommon in clinical practice but the central question as to 'what duration of anoxia or ischaemia defines the watershed between recovery of the tissue and extensive permanent injury?' has not been critically defined in man (Plum, 1973). Reasons for this include the lack of precise physiological data about a patient's cardiovascular and respiratory status at the time of a crisis since the immediate priority is resuscitation, and the inadequate neuropathological examination of the brains from fatal cases.

Postmortem examination of patients with severe hypoxic brain damage is usually carried out under warrant by the forensic pathologist who often feels obliged to slice the unfixed brain in the mortuary. Under these conditions it is impossible to recognize recent hypoxic brain damage up to and including frank cerebral infarction even when subsequent histological examination shows severe and extensive neuronal necrosis. When the brain has been properly dissected after adequate fixation (up to three weeks' immersion in buffered 10 per cent formol saline) an infarct of about 18 to 24 hours' duration may just be recognizable but even an experienced neuropathologist may fail to identify extensive diffuse hypoxic brain damage if it is less than some three to four days' duration (figs 1 and 2). The extent and severity of hypoxic brain damage can be identified and its distribution analysed only by the microscopical examination of many large, bilateral and representative sections of the brain. It is, however, often possible to establish that a patient has suffered hypoxic brain damage on the basis of a more restricted histological examination provided that the pathologist knows that certain parts of the brain are selectively vulnerable and is familiar with the cytological and histological appearances of ischaemic nerve cell change.

The identification of ischaemic cell change is made difficult in the human brain because of the frequent occurrence of histological artefact. The commonest artefacts are 'dark cells', 'hydropic cells' and 'perineuronal and perivascular spaces' (Cammermeyer, 1961). They are due partly to postmortem handling and to the slow penetration of fixative. Studies in experimental primates and in selected human material have shown that there is an identifiable process, namely ischaemic cell change, which is the neuropathological common denominator in all types of hypoxia.

The earliest histological stage of recent hypoxic neuronal damage in experimental animals in per-

Fig 1 Coronal section of brain from patient who survived 48 hours after cardiac arrest. There are no macroscopic abnormalities.

Fig 2 Same patient as in figure 1. Note subtotal ('laminar') necrosis of the third, fifth and sixth cortical layers with relative sparing of the second and fourth layers (darker staining). Cresyl violet. × 4.
further shrinkage of the nerve cell cytoplasm and the development of small, relatively dense granules lying on or close to the surface of the nerve cell (fig 3). Finally the neuron undergoes homogenizing cell change when the cytoplasm becomes progressively paler and homogeneous and the nucleus smaller. This type of change is most commonly seen in the Purkinje cells (fig 4) of the cerebellum. The time course of ischaemic cell change is relatively constant for neurons according to their size and site so that the interval between a hypoxic episode and death if between two and 18 to 24 hours can be assessed with reasonable accuracy. If the patient survives for more than 24 to 36 hours more advanced changes occur in neurons, and early reactive changes appear in astrocytes, microglia and endothelial cells. After a few days the dead nerve cells disappear and reactive changes become more intense, including the formation of lipid phagocytes, even though the latter may not appear if damage is restricted to neuronal necrosis. When survival is for more than a week or so the damaged tissue becomes rarefied due to loss of myelin and there is a reactive gliosis. Collagen and reticulin fibres are also laid own, the whole appearing as a glio-mesodermal reaction.

The differing susceptibility of nerve cells to hypoxia has been known for many years. According to Jacob (1963), 'in general the nerve cells are the most sensitive followed by oligodendroglia and astrocytes while the microglia and the cellular elements of the vessels are the least vulnerable'. Recent work suggests that local metabolic rather than vascular factors largely determine the pattern of selective vulnerability (Brierley, 1976).
1 STAGNANT HYPOXIC BRAIN DAMAGE
This is divided into two main types, viz, ischaemic and oligaemic.

Ischaemic
If the blood flow through an artery is arrested, e.g. by thrombus or an embolus, an infarct will develop within part or the whole of the distribution of the occluded vessel. The earliest macroscopic change is swelling of the infarct and its edges may be just discernible in the fixed brain within 12 to 18 hours. The lesion may be 'haemorrhagic' or 'anaemic' (fig 5) and at an early stage there is irregular, blotchy pallor of the affected cortex (fig 6). A sharp

and often very irregular line of demarcation between normal and abnormal myelin also appears early, the abnormal myelin staining palely (fig 7). A large infarct may swell sufficiently to constitute a space-occupying mass within 24 to 48 hours (Adams, 1966) resulting in tentorial herniation with secondary distortion of the mid-brain and infarction in the medial occipital (calcarine) cortex. The necrotic tissue is ultimately removed and replaced by a rather shrunken and cystic gliomesodermal scar.

A generalized arrest of blood flow to the brain is most commonly the result of cardiac arrest. This is usually a complication of some surgical procedure under general anaesthesia. Milstein (1956) estimated that about 300 deaths in the United Kingdom were caused by cardiac arrest related to surgery but by 1970 the number of such deaths had dropped to 100
per annum in England and Wales (Wylie, 1975), the difference in mortality being attributed to better methods of resuscitation.

If cardiac arrest is of abrupt onset and occurs in a patient at normal body temperature, complete clinical recovery is unlikely if the period of arrest is more than five to seven minutes (Brierley, 1972). A short period of cardiac arrest combined with periods of reduced cerebral perfusion pressure before or after the arrest may be as important as the duration of complete arrest (Miller and Myers, 1972) and may lead to accentuation of the ischaemic damage in the arterial boundary zones (Brierley, 1976).

If death occurs within 24 to 36 hours of the arrest, the brain, apart from a variable degree of swelling, may appear normal externally and on section even after adequate fixation. Within 36 to 48 hours it is sometimes possible to identify laminar or patchy discolouration in the depths of sulci, particularly in the posterior halves of the brain and selective necrosis in the Sommer sector of the Ammon's horn (fig 8a and b). Microscopy reveals diffuse neuronal necrosis with a characteristic pattern of selective vulnerability. Ischaemic damage is commonly greater within sulci than at the crests of gyri and is maximal in the third, fifth and sixth layers of the parietal and occipital lobes (fig 2). In the Ammon's horn the Sommer sector and endfolium are the most vulnerable (fig 9a and b).
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and b). These changes are sometimes associated with necrosis of the baso-lateral portion of the amygdaloid nucleus. The pattern of damage in the basal ganglia is less constant and tends to be most frequent in the outer halves of the head and body of the caudate nucleus, and in the outer half of the putamen. Damage in the globus pallidus may occur in all types of hypoxia but is especially common in carbon monoxide intoxication. Primary hypoxic damage in the thalamus is most common in the anterior, dorso-medial and ventro-lateral nuclei. In the cerebellum there is characteristically diffuse necrosis of Purkinje cells. Damage to the brain stem nuclei tends to be more severe in infants and young children than in adults.

Patients with severe diffuse brain damage due to cardiac arrest rarely survive for more than a few days (Bell and Hodgson, 1974) but occasionally they may remain alive in a persistent vegetative state for up to six months or longer (Brierley et al, 1971; Jennett and Plum, 1972). With increasing survival, the necrotic tissue is replaced by a gliomesodermal scar. When this occurs there may be an appreciable reduction in the weight of the brain and evidence of atrophy of both the cortical gyri and cerebellar folia. In coronal slices ventricular enlargement may be considerable. Whereas the cortex of the parietal and occipital lobes will be reduced to a thin band of discoloured tissue, often with a line of cleavage between it and the underlying white matter, that of the frontal and temporal lobes may appear essentially normal. While the parahippocampal gyri are usually normal, the hippocampi may show the features of Ammon's horn sclerosis. Even when cortical necrosis is severe and survival is for only a few weeks the thalami may appear grossly normal. Eventually evidence of retrograde degeneration will be seen in the corresponding thalamic association nuclei (fig 10).

Oligaemic
Because of autoregulation a moderate fall in cerebral perfusion pressure does not lead to a reduction in cerebral blood flow. However, when vasodilatation is maximal, autoregulation ceases and the cerebral blood flow will fall parallel to the perfusion pressure. Oligaemic brain damage due to systemic arterial hypotension conforms to one of three patterns (Adams et al, 1966), of which the first two types are the most common.

Ischaemic damage is concentrated along the boundary zones between the arterial territories of the cerebral cortex and in the cerebellum (fig 11). If the lesions are large and of several days' duration they can be recognized macroscopically provided that the brain is cut in the coronal plane (fig 12a). They vary in size from foci of necrosis in the cortex to large, wedge-shaped lesions extending from the cortex almost to the angle of the lateral ventricle. In the cortex, damage is most frequent and most severe in

Fig 10  Coronal section of brain from patient who survived for four years in a persistent vegetative state after cardiac arrest. The cortex is greatly narrowed and there is gross essentially symmetrical enlargement of the ventricles. The Ammon's horns and the thalami are also small.

Fig 11  Diagram to show arterial boundary zones in cerebral and cerebellar hemispheres. The right cerebral hemisphere is shown at three levels, viz, 1 = frontal, 2 = mid-temporal and 3 = occipital. Each boundary zone is stippled. ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, SCA = superior cerebellar artery and PICA = posterior inferior cerebellar artery.
the parieto-occipital regions, ie, in the common boundary zone between the territories of the anterior, middle and posterior cerebral arteries: it decreases towards the frontal pole along the intraparietal and the superior frontal sulci, ie, between the anterior and middle cerebral arterial territories, and towards the temporal pole along the inferior temporal gyrus, ie, between the middle and posterior cerebral arterial territories. The lesions are usually asymmetrical and may be unilateral, the pattern of ischaemic damage often being determined by atheroma and variations in the calibre of the vessels forming the circle of Willis. In the cerebellum the boundary zone between the territories of the superior and posterior inferior cerebellar arteries lies just beneath the dorsal angle of each hemisphere (fig 12b). There is variable involvement of the basal ganglia particularly in the head of the caudate nucleus and the upper part of the putamen. The Ammon’s horn and brain stem are usually not involved. While infarction in the cortical boundary zones may occur in the absence of ischaemic lesions in the basal ganglia and cerebellum the converse is not common.

On the basis of clinical evidence (Adams et al, 1966; Adams, 1974) and experimental studies on primates (Brierley et al, 1969) this type of brain damage appears to be caused by a major and abrupt episode of hypotension followed by a rapid return to a normal blood pressure. It is often seen after a conscious patient has collapsed as a result of a sudden reduction in cardiac output, viz, due to ischaemic heart disease, and it may occur in the anaesthetized subject during dental or neurosurgical procedures, particularly in the sitting position (Brierley, 1970). More recently it has been described following the use of methylmethacrylate bone cement (Adams et al,
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1972), in patients undergoing emergency treatment with antihypertensive agents (Graham, 1975) and in patients dying from blunt head injury (Graham et al, 1975). Because of the precipitate decrease in arterial pressure there is a transient failure of autoregulation and a severe reduction in CBF in the regions most removed from the parent arterial stems, ie, the boundary zones.

2 Ischaemic damage is generalized in the cortex of the cerebrum and cerebellum, is minor or absent in the hippocampi and is often severe in the thalami. The number of reported cases is small (Brierley and Cooper, 1962; Adams et al, 1966) but it would seem that this type of damage appears to be associated with hypotension of a relatively slow onset but of long duration.

3 Ischaemic damage is generalized in the cortex of the cerebrum and cerebellum but with variable accentuation along the arterial boundary zones. The hippocampi are usually spared and there is patchy damage in the basal ganglia. This type of damage appears to be associated with the abrupt onset of hypotension which is responsible for the accentuation of damage within the boundary zones followed by a sustained period of less severe hypotension which causes the diffuse damage.

2 ANOXIC AND HYPOXIC BRAIN DAMAGE

These terms imply that the blood leaving the lungs is either devoid of or has a greatly reduced oxygen content. Hypoxaemia of this severity will occur if there is obstruction of the air passages, after the inhalation of inert gases and in aviation accidents producing decompression. Even though it is still widely believed that brain damage can result from a simple reduction in the oxygen content of arterial blood, there is a lack of critical physiological data about cases purporting to show a correlation between neurological dysfunction and brain damage ascribed to the hypoxaemia. Indeed there is good experimental evidence in Rhesus monkeys and in baboons (Brierley, 1972) that the severity of the hypoxia required to produce brain damage also produces myocardial depression and a reduction in cardiac output. Thus, Brierley concluded that hypoxic hypoxia can produce brain damage only through the medium of a secondary depression of the myocardium, the pattern of damage being similar to that of oligaeamic hypoxic brain damage as described above.

3 ANAEMIC BRAIN DAMAGE

This occurs classically in carbon monoxide poisoning. The neurological complications of carbon monoxide poisoning are many (Garland and Pearce, 1967) but there is not a combination of neurological and psychiatric symptoms that can be regarded as the specific consequences of such poisoning since similar symptoms and signs may be encountered after cardiac arrest, hypoglycaemia, etc.

When death occurs within a few hours after poisoning, the organs display the pink/red colour characteristic of carboxyhaemoglobin. When survival is for 36 to 48 hours, the brain shows evidence of congestion, and petechiae are frequently seen in the white matter and the corpus callosum. Although there is a particular predilection for infarction of the globus pallidus in carbon monoxide poisoning (fig 13), there is also neuronal necrosis in other selectively vulnerable regions such as the Ammon's horn and the cerebral and cerebellar cortex.

Changes in the white matter are a common and often conspicuous neuropathological consequence of carbon monoxide poisoning. Damage to white matter tends to occur, particularly in patients who develop delayed signs of intoxication after a period of relative normality following acute poisoning.

Recent experimental work in the Rhesus monkey (Ginsberg et al, 1974) has underlined the importance of systemic circulatory factors in the production of brain damage, the concentration of damage in the white matter possibly being due to a combination of a toxic effect of carbon monoxide together with a moderate reduction in blood flow and perhaps an additional acidosis.

4 HISTOTOXIC BRAIN DAMAGE

The histotoxic effects of the cyanide ion and sodium azide are due to the inhibition of cytochrome oxidase. In acute intoxication death ensues rapidly from respiratory failure. In such cases the brain shows

Fig 13 Carbon monoxide poisoning. There is infarction of the superior pole of the globus pallidus (arrow). Celloidin section—myelin stain. × 1.6.
hypoglycaemia and multiple petechial haemorrhages. In longer surviving cases necrosis has been identified in the lentiform nucleus and in the cortex of the cerebrum and cerebellum (Brierley, 1976). Experimental studies have now shown that brain damage produced by either cyanide (Brierley, 1975) or azide (Mettler and Sax, 1972) cannot be attributed to histotoxic hypoxia alone but results from their secondary effects on respiration and circulation.

5 HYPOGLYCAEMIC BRAIN DAMAGE

Hypoglycaemia in man may lead to permanent brain damage. It may be due to an excess of insulin given either for the treatment of diabetes mellitus or psychosis and in rare instances of islet cell tumour of the pancreas and in examples of idiopathic hypoglycaemia in infants (Brierley, 1976).

In cases of short survival the brain may appear normal. There may be atrophy of the cortex and hippocampi and enlargement of the ventricular system in cases surviving for a number of weeks. Microscopy shows that the brain damage is very similar in type and distribution to that seen in ischaemic hypoxic brain damage, ie, nerve cell loss and a glio-mesodermal reaction in the striatum, the cortex and the hippocampus, except that there is often relative sparing of the Purkinje cells in the cerebellum.

Studies of hypoglycaemia in experimental animals have shown that ischaemic cell change is the principal neuropathological consequence of uncomplicated hypoglycaemia (Meldrum et al, 1971; Brierley et al, 1971a and b) and in longer surviving animals there is nerve cell loss and a variable glio-mesodermal reaction in the striatum, the cerebral cortex and the hippocampus (Kahn and Myers, 1971). These experiments show that the blood glucose level must fall to about 1 mmol/l (20 mg/100 ml) if uncomplicated hypoglycaemia is to produce brain damage, though a higher level of blood sugar may produce similar damage if complicated by some hypotension, hypoxaemia or epileptic activity. It is therefore quite possible that if a patient has been in hypoglycaemic coma for some time, both oligaemic and hypoxic factors may have contributed to the brain damage.

A different type of neuropathological change has been described in the human infant as a consequence of hypoglycaemia (Anderson et al, 1967). Neuronal changes were generalized and included chromatolysis with cytoplasmic vacuolization in some and fragmentation of nuclear chromatin in others. It has, however, been suggested that these appearances could be attributed to autolysis (Brierley, 1976).

6 FEBRILE CONVULSIONS AND STATUS EPILEPTICUS

Status epilepticus may be defined broadly as a convulsive episode lasting over an hour without an intervening period of consciousness (Corsellis and Meldrum, 1976). It has long been recognized as a serious danger to life at any age but it offers a special threat in childhood. The basic neuropathology is that of severe and diffuse ischaemic damage of stagnant hypoxic type in which there is widespread necrosis of the cortex, Ammon's horn, basal ganglia, thalamus, cerebellum and parts of the brain stem (fig 14). Thus status epilepticus, particularly in children, constitutes a medical emergency. Fortunately many patients make an uneventful recovery but some have a permanent intellectual or neurological deficit caused by hypoxic brain damage.

Experimental studies in subhuman primate (Meldrum and Horton, 1973; Meldrum and Brierley, 1973; Meldrum et al, 1973) have emphasized that several factors may contribute to the brain damage, eg, arterial hypotension and hyperpyrexia. Evidence of an impaired neuronal energy metabolism was also found due to a combination of excessive neuronal activity and accumulative effects of secondary changes such as hypoxia, hypoglycaemia, hypotension, etc.

Conclusions

Hypoxic brain damage may occur in diverse clinical situations where there is an inadequate supply of oxygen or glucose to nerve cells. Many patients who experience an episode of severe hypoxia die within a few hours when the pathologist will not be able to
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 identify any macroscopic abnormalities in the brain. If the patient survives for more than a few hours, however, varying degrees of damage are easily identified, particularly if the brain has been properly dissected after adequate fixation.

The identification of early hypoxic brain damage is made difficult in the human brain because of histological artefact. The earliest clearly identifiable structural damage is selective neuronal necrosis as shown by ischaemic nerve cell change with incrustation formation. If the hypoxic insult is more severe then frank infarction may occur. In each instance the necrotic tissue is replaced by a glio-mesodermal reaction.

The distribution of hypoxic damage is most easily assessed in large representative sections of the brain. It is not usually feasible for the general pathologist to undertake a comprehensive neuropathological analysis in every case of suspected hypoxic brain damage. Fortunately, however, it is possible to establish that a patient has experienced an episode of hypoxia sufficiently severe to produce widespread hypoxic damage by the histological examination of bilateral small blocks from the 'selectively vulnerable areas', namely, the arterial boundary zones, the Ammon's horns, the thalamus and the cerebellum.

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References


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