Editorial
The Diagnosis of Cerebral Death
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Sentience, speech, all the special qualities of man which place him at the apex of the evolutionary pyramid, are properties of his brain. More specifically, they are a function of the cortex. Physicians and public alike recognise that without a functioning brain there is no meaningful life, and it is now no longer necessary to debate whether the condition of 'cerebral death' is a just and entirely adequate description for the demise of a human being or vertebrate animal. The law reacting to the consensus has no real difficulty in coming to terms with this proposition. The principle has been embodied in the law or as part of the official regulations governing animal experimentation in most countries for a considerable period.

Although physicians have for long held this view on cerebral death in practice, it is only comparatively recently with the advent of intensive care, haemodialysis, organ transplantation, and the full panoply of supportive therapy that the traditional 'cessation of respiration and the beating of the heart' have become manifestly obsolete as a definition of death. The report of the Harvard Committee (Beecher et al, 1968) on the definition of cerebral death represents a turning point in the acceptance of these views. Earlier accounts of recovery of brain function in apparently hopeless situations which were inadequately defined are no longer relevant. We now have enough knowledge and experience to justify proper criteria to define the conditions in which cerebral death may be deemed to have occurred. These criteria are quite clear and it is really not a difficult clinical decision when these conditions are met.

The attention focused on the diagnosis of cerebral death has tended to isolate discussion on this subject from the general context of medicine of which it is a part. There is a desire to formulate inflexible rules which are alien to the practice of medicine in all other spheres. In other clinical circumstances, decisions affecting the life and death of patients are made on
the basis of clinical judgement and experience taking into account all the details of each particular and unique situation and utilising the total knowledge of the doctors concerned. It is rare that we can establish a rule which is appropriate to all circumstances and the element of judgement is never excluded. The desire to create inflexible rules in this particular instance arises from emotive discussions, the immediacy of the consequence of one's decisions and the natural tendency to retreat behind a rigidly prepared and manifestly defensible position. Unfortunately life is not like that. One cannot suspend clinical judgement.

As will be described, there are rules which work, but slavish adherence to them leads on the one hand to loss of viable organs whilst the doctor observes the failing circulation of the cerebrally dead for a 'legal' twelve or twenty-four hours, and on the other promotes the vegetative existence of the severely brain damaged. Whilst the former simply requires a sense of proportion, the latter is far from easy to resolve.

We must all have made errors in this respect: persisted with the hopeless case only to be rewarded with a hapless travesty of a human being, a burden on family and resources but rarely on themselves. With experience, it is rare now to find recovery much better than expected. There is a natural tendency to err towards 'the benefit of the doubt'; it is in the nature of our training as physicians and of the morality of our Western civilisation. I think we would rather have it this way but it is reasonable to question the morality of the survival of the severely brain damaged even if there are no ready answers. For the time being at any rate, it is a matter of judgement based on experience. We do not have the techniques available which can give sufficiently firm data from which to assess the potential recovery of a partially damaged brain. There are some guidelines — the age, the nature of the pathology, rate of regression, nature of complications and so on, as will be discussed, but there are no rules.

The assessment of the condition of cerebral death falls naturally into two stages:

1. The Antecedent Conditions

The patient will be in coma and usually on a respirator. Unless this is so, the question of cerebral death is premature and outside the present discussion, but great emphasis is to be placed on the time course of events and the proper assessment of the neurological status leading to the terminal state. The diagnosis must be established beyond reasonable doubt and must be the sufficient cause of the patient's state and irremediable. It is necessary that treatable conditions such as cerebral infections, and extra-dural and sub-dural haematomas in the case of head injury, have been excluded or that the cerebral state has deteriorated despite adequate treatment. One must be
assured that the clinical state is not immediately caused by prevailing toxic or metabolic factors. Whilst these conditions may well produce neuronal death secondarily by anoxia, they rarely do so directly (cyanide poisoning and hypoglycaemia are two notable exceptions). In general, systemic metabolic and toxic disorders cause death by cardiac failure rather than by their cerebral effects: brain function may be suspended without neuronal death but suspension of cardiac function is obviously catastrophic. Recovery from drug overdose coma simulating cerebral death is well known (Bird & Plum, 1968). It should be borne in mind also that the effects of depressant drugs and toxins are enhanced in cerebral anoxia and in brain damage so that cerebral damage cannot be properly assessed so long as these depressants remain in effective concentration in the tissues. In general, therefore, systemic metabolic and toxic factors are insufficient causes alone to support a diagnosis of cerebral death.

Since the problem of determining cerebral death with any degree of urgency in practice arises only with those cases likely to provide donor material for transplantation, the causes are likely to be restricted to those having clear structural effects on the brain — expanding intracranial lesions, haemorrhage and infarction, and head injury for example — and anoxia. The diagnosis and time course of these conditions are well known. The direct cause of cerebral death is brain tissue hypoxia, although the mechanisms may be different in each.

The brain and the heart are the highest consumers of oxygen per unit mass of all the body organs and the most vulnerable to anoxia. The brain has low energy resources, a relatively sparse tissue capillarity and its oxygen consumption is disproportionate to its blood supply — it has been well said to be normally 'on the brink of anoxia'.

Recent work by Hossman and Sato (1970) and others (reviewed in Siesjö & Plum, 1973) suggests that neurones are probably rather less directly vulnerable to anoxia than was previously thought and that it is the capillary responses to anoxia which constitute the weak link. Thus even low rates of blood flow (12% of normal in the cat) in the capillaries are sufficient to prolong neuronal viability past the point where they have ceased to function electrically. But complete ischaemia of more than seven minutes produces capillary endothelial cell swelling which results in 'no reflow' at capillary level when the central flow is re-established, leading to persistent tissue anoxia and cell death (Chiang et al., 1968; Ames et al., 1968). From a clinical point of view, whilst a systolic pressure of 60-70mm mercury is sufficient to maintain a normal brain, this pressure is probably inadequate to re-establish capillary perfusion after total ischaemic anoxia of several minutes, eg cardiac arrest, when pressures of twice this value are more appropriate if further deterioration is to be avoided. The vicious circle: capillary endothelial
swelling — anoxia — tissue oedema — reduced blood flow — increased swelling — probably accounts for the subsequent deterioration of patients surviving successful cardiac resuscitation. The brain is particularly susceptible to stagnant (no flow, or ischaemic) anoxia whereby the accumulation of the lactic acid, product of anaerobic glycolysis and retained CO₂ in the tissues further reduce viability (Siesjö & Plum, 1973).

Space occupying cerebral pathology produces secondary anoxic effects by displacement of intracranial contents ('pressure cones' — see below) and it is not until intracranial pressure reaches about two-thirds of systemic arterial pressure that cerebral perfusion ceases (Walker, 1969). Brain tissue oedema secondary to trauma produces ischaemic (stagnant) anoxia.

2. Assessment of the Cerebral State

The content of consciousness depends on the cerebral cortex. There exists, however, a system of neurones, the reticular activating system (Magoun, 1963) consisting essentially of the central grey matter core extending from the upper third of the pontine tegmentum rostrally through the midbrain into the diencephalon, which has the property of determining the state of alertness of the brain. Malfuction of this region from whatever cause results in loss of consciousness and coma. Cortex and brain stem interact and massive cortical dysfunction, particularly when it is of sudden onset and involves the dominant hemisphere, is usually associated with temporary loss of consciousness. Sub-acute or chronic cortical loss alone produces dementia rather than coma. Decorticate 'thalamic' man can hardly be considered conscious, but on the other hand does show 'waking' and 'sleeping' patterns which are not apparent when the midbrain reticular system is destroyed. Persistent and deep coma always supervenes on destruction or blockade of this region.

However, for the state of coma to persist, the malfunction in this area must be both extensive and bilateral: acute partial lesions may result in coma from which recovery is possible. It is generally true that acute neurological insults have considerably more profound functional effects than equivalent chronic lesions. An acute lesion may however apparently progress by the effects of tissue oedema so that the neurological deficit appears worse after several hours rather than better. Generally some signs of the abatement of what might be termed the neurological 'shock' effects of an acute lesion (which is certainly much more complicated than can be accounted for simply by neurogenic deafferentation) should be apparent in twenty-four hours but oedema can persist very much longer. These factors must be taken into account when assessing prognosis.

Coma resulting from the effects of intracranial expanding lesions not directly involving the midbrain is due to pressure and distortion of the brainstem at the tentorial opening usually associated with the formation of pressure
cones (medial temporal lobe from above, cerebellum from below) causing ischaemia of the reticular formation core. If this persists for more than a few hours recovery becomes increasingly unlikely.

In global cerebral anoxia, the evolutionary older parts of the brain are more resistant and the 'last to go', the neocortex being the most vulnerable. Persisting coma in these circumstances therefore is likely to be associated with severe cortical damage and this is borne out in clinical practice (Brierley et al, 1971). The blood supply to the midbrain reticular core is through the small vessels of the posterior perforated space lying between the peduncles and derives from the posterior cerebral arteries just distal to their origin at the basilar artery, and from the posterior communicating arteries of the circle of Willis. Detail variations in the supply probably account for the varying degrees of coma seen with occlusion of the basilar artery on the one hand and the carotid on the other, and transient disturbances of flow in the circle of Willis due to vascular spasm are probably a better explanation of the transient coma associated with cerebral haemorrhage than is neurogenic 'shock' referred to earlier.

Because of the area of doubt which exists in determining how much of the activating brainstem system is permanently incapacitated in a patient in coma, this state is rarely sufficient in itself to determine a fatal prognosis except perhaps where there is established malignant pathology. If it is demonstrated also that the lower brainstem is non-functional (lesions of the brainstem caudal to the upper mid-pontine level, ie pre-trigeminal nerve, do not cause coma) then the lower extent of the pathology is established, additional vital functions are lost and the problem is resolved.

The detailed examination of brainstem functions has been described elsewhere (see Plum & Posner, 1972; MacGillivray, 1972) and only the essentials need be given here. The principles simply depend on testing a number of reflex pathways which arise in, or cross the brainstem, and provided they are all absent it can be safely concluded that there is no functional brainstem between the lower medulla and the upper midbrain.

The observations are:

1. The patient is in unrousable coma.

2. The eyes should be in mid position (excepting pre-existing squints) and stationary, ie there are no spontaneous or tonic inputs to IIIrd, IVth and VIth nerves (the Ist and IIId cranial nerves are not testable).

3. The eyes should not move in the eyesockets on brisk turning of the head to one side or the other, nor on flexion, ie there are no doll's head eye movements (oculocephalic responses). These occur when cortical influences are absent, thus 'releasing' the lower 'centres' for eye movement, but afferents from the neck and vestibular apparatus operating through
the pontine and mesencephalic gaze centres, the medial longitudinal bundle and the IIIrd, IVth and VIth cranial nerves, cause brief movements of the eyes in the direction opposite to that of rotation or tilt when the head is moved quickly.

4. The pupils should be stationary and in mid position (3-4mm) and non-reactive to light, i.e., there is no tonic parasympathetic (constrictor) or sympathetic (dilator) input to the eye and the reflex path, retina — geniculate body — superior colliculus — Edinger-Westphal (pupillo-constrictor) nucleus of nerve III, is not operative. In practice it is often the case that some residual parasympathetic (small pupils) or sympathetic (dilated pupils) effect persists when other brainstem functions are lost and pupil size is not an absolute criterion.

5. The corneal reflex is absent and there is no response to supra-orbital pressure or pinching the cheek and lips, i.e., sensory Vth nerve — VIIth nerve. The jaw jerk is absent (Vth nerve).

6. The face is flaccid with no spontaneous movements or responses to painful stimuli elsewhere — i.e., VIIth nerve.

7. There will be no response to loud noises. The vestibular component of the VIIth nerve is readily tested by irrigating the auditory canal with 20ml of iced water by means of a small catheter and syringe directing the water flow upwards towards the skull vertex. Nystagmus (oculo-vestibular response) produced in this way indicates an intact connection between the vestibular apparatus, vestibular nucleus, intranuclear ocular connections, and the IIIrd and VIth nerves. The response must be absent.

8. The lower cranial nerves are tested simply by the absence of any response to glottal stimulation and tracheal aspiration. There should be no change in pulse rate on eyeball compression (Xth nerve).

9. There should be no spontaneous respiration. Disconnection of higher influences from the respiratory nuclei produces various forms of abnormal periodic or rhythmical breathing patterns, whereas local medullary disturbances produce erratic 'chaotic' respiration and apnoea (lateral lower medulla). Low pCO₂ values also produce apnoea and one must be assured that CO₂ levels are reasonable; no breathing response after the respiratory has been switched off for three minutes is an adequate test.

10. There must be no transmission between higher cerebral structures and spinal cord, i.e., no purposeful or spontaneous movements. Decerebrate attacks with periodic extension of all limbs indicate transection
above the mid-pontine level with residual function at the level of the vestibular nuclei (VIIIth nerve). The plantar responses will be extensor or absent. Spinal reflex activity can be quite brisk and is of no diagnostic significance in this situation.

11. Most of the tests mentioned depend on motor responses. Muscle relaxants clearly preclude such examinations. It is necessary to exclude the influence of drugs, toxic effects and metabolic disturbances, all of which can simulate or aggravate brainstem insufficiency.

12. It is accepted practice to repeat the observations at six, twelve or twenty-four hours, and whilst this is a reasonable precaution when there is any doubt about the findings, the pathological process or the time course of events, it is usually the case that these are well known. In the author’s view it is not necessary to adopt a rigorous protocol of this nature if the patient has been followed through a steadily deteriorating time course.

Given the appropriate antecedent conditions, the absence of brainstem function, as tested above, for a period exceeding six hours or longer can be taken as unequivocal evidence of cerebral death on clinical grounds. It is unnecessary to dispute the viability of the cerebral cortex in these circumstances. Brainstem death precludes independent existence, and indeed is rapidly followed by a failing and unresponsive circulation. In practice, by the time these conditions are met, cerebral activity as indicated by the EEG is usually absent or barely detectable and post-mortem examinations confirm extensive cerebral softening (Alderete et al, 1968).

Coma and massive cerebral destruction can occur, however, in association with a reasonably intact lower brainstem. The medulla is more resistant to anoxia than either the midbrain or cortex which is the most vulnerable. Patients in this category are usually those who have had a severe head injury or survived prolonged systemic anoxia and they constitute a group in whom the prognosis is extremely difficult to make. The chronically comatose and demented survivors of resuscitation are to be found amongst these patients.

There are some pointers which are helpful. Age is an important factor: the recuperative powers of the brain and the ability to withstand anoxia without permanent damage is high in the young. It is rare to find a permanently comatose child, but on the other hand severe dementia, epilepsy and spasticity and abnormal movements are not that uncommon. An adult, particularly past middle age, who remains in coma twenty-four hours after apparently successful cardiac resuscitation will certainly be demented if consciousness is regained — a reflection of the greater vulnerability of the cortex to anoxia. The evaluation of the effects of head injury can be very difficult. The problem
is reviewed by Carlson et al (1968). Profound and persistent coma carry a bad prognosis.

In severe coma, the function of the cortex is effectively inaccessible to clinical evaluation. In these circumstances the EEG can be an extremely valuable adjunct to the clinical assessment. A 'flat' EEG recorded in appropriate circumstances at high gains and under stringent conditions (MacGillivray, 1972; Silverman et al, 1970) and persisting for twelve hours or more is conclusive evidence of cerebral death. A deteriorating EEG pattern following an anoxic episode carries a poor prognosis, and the presence of persistent generalised epileptic spiking unchanged over twenty-four hours and which persists for weeks, invariably indicates an irrecoverable cortex.

When all is said and done, however, in the presence of unequivocal features of cerebral death, ie an adequate pathology, the absence of all signs of brain-stem function when the action of depressant drugs, toxic and metabolic effects and hypothermia are excluded, and no evidence of cerebral activity on repeated EEG examinations, then there remains an area of doubt about the outcome which may only be resolved by time alone. The problem admits of no simple solutions but continuing experience and the accumulation of careful clinical observations will gradually reduce uncertainty in the future. There is an obligation on all of us to ensure the fullest possible documentation of these problems for future reference.

IN SUMMARY

The conditions sufficient for the diagnosis of cerebral death are as follows:

1. The clinical diagnosis must be established beyond reasonable doubt and irremediable.

2. The cause of the patient’s cerebral state must be such that cerebral death is a known consequence (generally structural damage and anoxia) and there is evidence of progressive deterioration.

3. The patient is in unrousable coma and makes no purposeful movements; there is no response to stimuli above the neck and no purposeful or coordinated response to stimuli of the limbs or body. The plantar response is extensor or absent.

4. There is no detectable function in any of the cranial nerves and brain-stem reflexes (oculocephalic and vestibulo-ocular) are absent; independent respiration is absent.

5. Prevailing toxic, drug or metabolic effects, hypothermia(<35°C) and hypotension (<60mm mercury unless known to be unresponsive and failing) are not sufficient to account for the clinical state.

These conditions are adequate alone. In addition, given the appropriate
clinical circumstances, i.e. 1, 2, 3, 5, above then cerebral death is also accepted if:

6. An EEG carried out under adequate conditions (trained personnel, high gains, time constant of 0.3 seconds, recording from all parts of the head and for at least thirty minutes) and repeated in four to six hours, shows no significant cerebral activity; or

7. Cerebral blood flow is demonstrated to be absent by adequate contrast radiography or other generally accepted methods.

So far as the author is aware, there are no reported exceptions to these conditions.

REFERENCES

Bird, T. and Plum, F. (1968) Neurology, 18, 456
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