ABC of Brain Stem Death

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DIAGNOSIS OF BRAIN STEM DEATH—I

Preconditions

There are three steps to making a diagnosis of brain stem death: (a) ensuring that certain preconditions have been met; (b) excluding reversible causes of apnoeic coma; (c) confirming brain stem areflexia and persistent apnoea. If every case is approached systematically errors should not occur. The aim of specifying preconditions and exclusions is much more subtle than is immediately apparent. They serve as a double filter. Once attention has been given to the preconditions and the exclusions, absence of brain function implies an irreversible state of affairs. "When near-misses are alleged, it usually transpires that the preconditions have not been stringently applied, rather than that tests had been inadequately performed."¹

Two preconditions are necessary: (a) that the patient is in apnoeic coma—that is, unresponsive and on a ventilator—and (b) that the cause is irremediable structural brain damage due to a "disorder which can lead to brain death." Several of these terms need elaboration.

Coma is used in the accepted sense as a state of sleeplike unresponsiveness from which a patient cannot be roused. Such patients fail to open their eyes spontaneously, express no comprehensible words, and neither obey commands nor move their limbs to localise or resist painful stimulation^{2 3} (apnoeic coma, of course, precludes the possibility of testing phonation). That the patient is on a ventilator should be self-evident. The accurate determination of apnoea will be discussed later.

A positive diagnosis of a disorder that can lead to brain death depends on standard methods of history taking, clinical examination, and special investigation. Severe head injury and subarachnoid haemorrhage (which together account for about 80% of cases of brain stem death) are normally easy to diagnose. The patient is alert and well before rapidly becoming comatose. A history of cardiac arrest, strangulation, or drowning is not hard to establish either. If the primary diagnosis cannot be established the patient has not even approached the first hurdle: meeting the preconditions.

The objective is not only to diagnose a condition that could damage the brain but to establish that it has done so irremediably. The *irremediable* nature of the disorder is only partly assessed by the severity of the clinical features (apnoeic coma is always a critical state). In theory, "irremediable" means that no treatment may reasonably be expected to change the condition. In practice, it also means that no therapeutic endeavours (such as resuscitation or measures directed at controlling cerebral oedema) have changed the patient's condition during an adequate period of observation and that further endeavours are therefore unlikely to be effective. The passage of time is an essential component in determining that a lesion is irremediable; without it the term could easily become self-serving.

Some remediable conditions may temporarily cause more severe neurological deficits than some irremediable ones. Subdural or extradural haematomas are potentially remediable. Massive intracerebral haemorrhage or gross destruction of the brain after trauma is not. Cerebral oedema may be remediable in its early stages but not after various mechanisms come into play, which reinforce its effects.

The responsible disorder may be thought of as *structural* when it is not due to such functional—that is, potentially reversible—causes as drug intoxication, hypothermia, or metabolic or endocrine disturbance. The structural nature of the disorder can usually be inferred from the history

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and clinical examination or established by direct inspection, imaging, or other investigations. Does establishing a diagnosis of structural brain disease necessarily imply visualising a lesion, or is inference of its structural nature enough? In a few cases cerebral oedema, reduction in ventricular size, or shifts due to brain swelling will have been shown by imaging or at surgery. Occasionally an open wound discloses the state of affairs. If the lesion is a subdural or extradural haematoma or an intracerebral haemorrhage there will, of course, be no problem.

Postanoxic oedema is another matter. The UK code rightly assumes that preconditions have been met when patients remain in coma and apnoeic for several hours after "successful" cardiopulmonary resuscitation. But trying to subsume the responsible lesions under the heading "structural" introduces unnecessary ambiguity.

Exclusions

- Hypothermia ($<35^{\circ}\text{C}$)
- Drug intoxication
- Metabolic or endocrine disturbance

Coma: Duration of drug effects

Alcohol metabolism (zero order kinetics) 10 ml/h

Plasma half lives (in hours):

Aspirin	0.25-0.30
Pentazocine	2
Paracetamol	2-4
Diphenhydramine	4-10
Imipramine	8-24
Morphine	10-60
Nortriptyline	15-93
Methadone	18-97
Pentobarbitone	20-35
Chlorpromazine	23-37
Phenytoin*	24 (mean)
Carbamazepine	24-48
Diazepam and active metabolites	24-96
Phenobarbitone	50-140

*Prolonged at high concentrations

*The plasma half lives of drugs show large intersubject variation. This is particularly true for lipid-soluble drugs such as phenytoin and nortriptyline, which are eliminated by oxidative metabolism. The source of this variability is both genetic and environmental (the plasma half lives of several drugs may be reduced in chronic smokers). With some drugs (the best example is again phenytoin) the plasma half life increases with increasing plasma concentration because of saturation of the drug-metabolising enzymes. Furthermore, the comatose state itself may impair drug metabolism and hence prolong plasma half lives.

Drug intoxication, hypothermia, and metabolic or endocrine disturbances may all cause profound yet reversible changes in brain stem function. The UK code is unambiguous: brain stem death should not be considered in the presence of these conditions, whether they are primary causes of the coma or possible contributory factors.

Acute intoxication is the commonest condition that needs to be excluded. Apart from head injury it is probably the commonest cause of a sudden coma lasting more than six hours in a previously healthy young adult. It is certainly the commonest cause of a deep coma, of fairly rapid onset, still defying diagnosis 12 hours after admission to hospital. The initial history, obtained from relatives, is often unreliable. Most such patients will, of course, lack evidence of structural brain disease. They will therefore not have crossed the "preconditions" hurdle.

Problems may arise when the patient's state is suspected of being due to the combined effects of trauma and drugs. Common sense and clinical judgment are required. The circumstances are crucial. A depressed elderly woman living alone and found unconscious at the foot of the stairs with a fractured skull is a different diagnostic problem from the climber who has slipped and sustained a similar fracture. A boxer knocked out in a ring and later lapsing into coma and a patient in hospital having a second subarachnoid bleed are easier to assess than the drunk who has fallen and knocked his head as he lurched out of a pub. Alcohol is the commonest (but only temporary) cause of diagnostic problems. The neurological effects of acute intoxication last no more than six to eight hours.

If intoxication is suspected it is important to keep in mind the approximate plasma half lives of various coma-producing drugs and to remember that—as a clearance procedure—blood concentrations may lag significantly behind brain concentrations.* When toxicological facilities are not available—and there can be few major centres in the UK with facilities for ventilatory support but no access to a drug screening centre—it is reasonable to allow about three days to elapse for things to sort themselves out. There is no urgency about making a diagnosis of brain stem death, unless the circumstances are absolutely clear cut. In practice trauma plus significant drug intoxication (other than alcohol) is rare.

Physicians are still occasionally called to assess patients in intensive care units only to find that they are still under the influence of drugs blocking neuromuscular transmission. Efficient neuromuscular blockade will, of course, both produce apnoea and abolish most or all brain stem reflexes. The doctor called to the intensive care unit must always look at the drug sheet before testing for brain stem death.

If the patient has retained knee or ankle jerks he cannot be under the influence of neuromuscular blocking drugs (the converse is not true). Very occasionally, owing to rare inherited enzyme deficiencies, the neuromuscular blockade may be prolonged. Doubts can be resolved (slowly) by allowing time to pass or (more promptly) by resort to a simple nerve stimulator. In patients with brain stem death there is no neuromuscular blockade. The peripheral nervous system is not affected. Regular electrical stimuli applied to major nerve trunks will result in regular contractions of the muscles they supply.

Importance of timing

Examples of observation periods on ventilator, before testing.	
	hours
Apnoeic coma after	
(a) major neurosurgery	
(b) angiographically proved aneurysm; second subarachnoid bleed (in hospital)	>4
Head injury (without secondary brain damage from haematoma, shock, or brain hypoxia)	>6
Spontaneous intracranial haemorrhage (without secondary hypoxic brain damage)	>6
Brain hypoxia (anaesthetic accident, cardiac arrest, drowning, etc)	>24
Any of the above (when suspicion of additional factor of drug intoxication, and no screening facilities)	50-100

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The UK code gives only general guidance on timing. This is as it should be. The "time before testing" (the time on the ventilator) is the time it takes to satisfy the preconditions—that is, to establish an unequivocal diagnosis of structural brain damage and become certain that the condition is irremediable. An unhurried approach is the best safeguard against premature or unjustified suspicions of brain stem death.

The various clinical scenarios have been graphically described¹ but are worth recapitulating.

(1) When the patient develops persistent apnoeic coma in hospital—for example, after major neurosurgery or after a second bleed from an angiographically proved aneurysm—testing can be performed within a few hours.

(2) After a head injury immediate apnoea may develop. Most such patients die but occasionally artificial respiration is given at the scene of the accident. The patient may then recover spontaneous breathing for a few minutes. If apnoea develops after admission to the ward (secondary apnoea) the patient will usually be put on a ventilator, while vigorous measures are taken to overcome the effects of hypoxia, shock, or cerebral oedema. Time must be allowed for these measures to take effect and for a raised blood alcohol concentration (if present) to subside below coma-producing concentrations. It takes several hours to ensure that the responsible lesion is "irremediable." Testing for possible brain stem death in such cases is best deferred for at least six to 12 hours.

(3) Diagnosing spontaneous intracranial haemorrhage (either subarachnoid or intracerebral) is usually straightforward, although accurate assessment may take several hours. Immediately after a first subarachnoid haemorrhage (or even occasionally after a second bleed) reversible apnoea may develop, lasting from a few minutes to an hour or so. When secondary apnoea develops after several hours in a case of intracranial haemorrhage the prognosis is grave, as a pressure cone has probably developed. Both intracranial and subarachnoid haemorrhage may lead to brain stem death, but it will take over six hours for the diagnosis of irremediable, structural brain damage to be unequivocally established.

(4) When a patient has suffered cerebral hypoxia after cardiac arrest or an anaesthetic accident the degree of brain damage may vary enormously. Even when the hypoxia has been severe (due to difficulties or delays in resuscitation) a vegetative state is a more common outcome than brain stem death. Persistent myoclonic seizures may develop within hours of the anoxic insult, and the effects of anticonvulsant medication may then preclude reliable testing for irreversible loss of brain stem function. Recurrent episodes of hypotension or cerebral ischaemia may occur. Assessment may prove difficult. The UK code points out that "continuity of clinical observation and investigation" may be necessary before there is certainty that the preconditions have been fulfilled. This may take much longer than in cases of uncomplicated head injury, although there is now good evidence that the neurological prognosis after resuscitation from cardiac arrest (both in relation to brain stem death and to other forms of brain damage) may be ascertained earlier.^{4 5}

(5) Observation for three to four days may occasionally be necessary when there is doubt about the possible contributory role of drugs (other than alcohol) or other confusing factors, such as hypothermia or metabolic upset. If the brain stem is dead many patients will develop asystole during this period. Cases in which the primary diagnosis is drug intoxication—that is, where there is no evidence of structural brain damage—will not, of course, have fulfilled the preconditions.

In each of these cases it is clearly up to the physician in charge to determine whether longer periods are necessary.