

# Brain death

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Since the Harvard report of 1968, the concept of brain death has become widely recognized throughout the world. Most developed countries have accepted brain death as constituting death of the individual, and allow such patients to be used as ‘heart-beating’ organ donors. Although the US and most other countries accept a ‘whole-brain’ definition of brain death, the concept of *brainstem* death has been adopted in the UK. This article describes the UK diagnostic criteria in detail, and compares these with the criteria used in other countries. Management of the brain dead organ donor is described, and controversies relating to the concept of brain death are also discussed.

**Key words:** brain death; ethics, medical; organ procurement; organ transplantation

... the two essential components of human life (the capacity for consciousness and the capacity to breathe) depend on the integrity of these few cubic centimetres of [brainstem] tissue. (Pallis and Harley, 1996)

There’s a big difference between mostly dead and all dead. Now, mostly dead... is slightly alive. (Miracle Max, as quoted by Van Norman, 1999)

You’re dead when your doctor says you are. (Newsweek, December 1967)

## Introduction

The diagnosis of death has always been fraught with difficulties. In previous centuries, many peculiar methods of confirming death were suggested (Powner *et al.*, 1996). These included observation for the gradual rusting of a needle inserted into the biceps, the movement of needles with flags attached inserted transcutaneously into the heart, and absence of organ movement on X-ray fluoroscopy. The fear of premature burial

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prompted the sale of coffins linked to a bell, which would ring above ground if the occupant started to breathe. Even in modern times, the diagnosis of death is not always straightforward (Charlton, 1996).

The advent of modern resuscitation and intensive care in the 1950s and 1960s, however, brought new problems. Patients with severe and permanent brain damage, who might previously have died from respiratory failure and airway problems, could now be kept alive by mechanical ventilation. The most severe of these cases would have permanent loss of consciousness, absence of brainstem reflexes, and complete loss of respiratory drive – the clinical condition now known as ‘brain death.’

Most cases of brain death are due to head trauma or spontaneous intracranial haemorrhage. These conditions may lead to herniation of the brainstem through the foramen magnum (‘coning’), due to severely raised intracranial pressure. Less often, brain death is caused by severe cerebral hypoxic-ischaemic events, such as after prolonged and/or inadequate cardiopulmonary resuscitation. Brainstem vascular events (infarction or haemorrhage) may lead to primary death of the brainstem, with identical clinical features.

Since the late 1960s, most developed countries around the world have adopted the concept of brain death, and equated it legally to ‘cardiorespiratory death.’ However, an undercurrent of controversy remains about several aspects of this concept, both in

medical and lay circles. After more than 30 years, the issue of brain death is truly 'well settled yet still unresolved' (Capron, 2001).

Although the UK has accepted a conceptual definition of *brainstem* death, most other countries have adopted the US concept of 'whole-brain' death. For this reason, the term 'brain death' is used throughout this article except when referring specifically to the UK situation. The clinical signs are identical for each, and the implications of this conceptual difference are discussed later.

## History

### Early concepts of 'neurological death'

In 1959, Mollaret and Goulon described a number of patients in a condition they called *coma depasse*, or 'beyond coma.' Apart from unconsciousness, these patients showed apnoea, loss of brainstem reflexes, and other abnormalities (such as hypotension, presumed diabetes insipidus and disturbances of temperature regulation) consistent with the modern concept of brain death (Pallis and Harley, 1996).

This, among other things, led to challenges to the traditional cardiorespiratory criteria for diagnosing death. The advent of cardiopulmonary resuscitation and cardiopulmonary bypass, and later heart transplantation, showed that cessation of the heartbeat (even if permanent) was not sufficient to cause death. In a legal context, the then Home Office pathologist, Professor Keith Simpson, had suggested in 1964 that 'there is still life so long as a circulation of oxygenated blood is being maintained to live vital (brainstem) centres' (Simpson, 1968). Therefore, cardiorespiratory criteria came to be seen as relevant only because they showed *indirectly* that irreversible loss of brain function had occurred.

The concept and original definition of brain death is often ascribed to the Harvard report of 1968 (see next section). However, for several years before this, neurological definitions of death had been suggested, and organs removed for transplantation from patients after the fulfillment of such criteria (Mohandas and Chou, 1971; Rutecki, 1994; Powner *et al.*, 1996; Giacomini, 1997). The concept of 'brain death' had therefore been recognized, although the term was not in general use, and diagnostic criteria were still under debate. There was also a lack of consensus whether death should be redefined at all. Without such a

redefinition, the ethical and legal objections to organ procurement from such patients were obvious.

The world's first human heart transplant was performed in South Africa in 1967, and the second such transplant followed later the same month. Hoffenberg (2001) describes how he was asked to pronounce 'dead' the patient who subsequently became the donor for the second operation. This patient was unconscious, having suffered a subarachnoid haemorrhage. At that time, there were still no widely accepted guidelines for such a diagnosis of death, and Hoffenberg describes his unease as he 'stood at the bedside of [his] patient wondering what on earth to do...' In the event he declined to pronounce death, as a few neurological reflexes could still be elicited. ('God Bill, what sort of a heart are you going to give us?' the professor of surgery had said.) By the following day the reflexes had disappeared, and the transplant went ahead.

It is important to note that ventilation was first discontinued in these heart donors, and the hearts removed only *after* cessation of heartbeat (Ozinsky, 1967). Presumably, to do the reverse would have been seen as too radical at that time. In fact, the medical staff involved were somewhat reticent (in the lay press) about admitting even that ventilation had been withdrawn (Giacomini, 1997).

Why did the first human heart transplants take place in South Africa, and not in any other country? In the US, animal research in this area was far more advanced, but ethical and legal concerns had prevented its extension to humans. Hoffenberg suggests that (among other reasons) the climate of opinion in South Africa was more permissive, and more ready to accept 'neurological death' in the absence of recognized guidelines. At any rate, the subsequent ethical controversies provided an urgent stimulus for the development of such criteria.

### The 'Harvard criteria'

In 1968, an Ad Hoc Committee of the Harvard Medical School issued a landmark paper entitled 'A definition of irreversible coma,' subtitled 'Report... to examine the definition of brain death' (Harvard, 1968).

Apart from establishing the phrase 'brain death' in common use, this report achieved three things. First, it offered a simple *conceptual definition* of brain death – a 'permanently non-functioning brain.' (The shortcomings of this rather simplistic definition would become apparent in later years, as discussed later.) Second, it described a set of characteristics, or *diagnostic criteria*,

by which this state could be recognized. Third, it proposed a *redefinition of death* to include this state – in other words, that brain death should be considered legally equivalent to death, despite continued functioning of the heart and other organs. Patients could then be declared dead *before* being taken off the ventilator, to ‘provide a greater degree of legal protection to those involved.’ As stated boldly in the opening sentence: ‘Our primary purpose is to define irreversible coma as a new criterion for death.’

The diagnostic criteria specified were: complete unresponsiveness to external stimuli; the absence of brainstem reflexes; the absence ‘as a rule’ of tendon reflexes; and apnoea. The latter was to be tested for by turning off the ventilator for three minutes (although no mention was made of the need to prevent hypoxia during this test). An isoelectric electroencephalogram (EEG) was said to be of ‘great confirmatory value,’ and ‘when available . . . should be utilised.’ Hypothermia and the effects of central nervous system depressant drugs were to be excluded before testing, and the tests were to be repeated after at least 24 hours to ensure there was no change. Unfortunately, there was no mention of the need to establish a definite cause of irreversible structural brain damage before testing.

Giacomini (1997) gives a fascinating insight into the background to the Harvard report, and the workings of the committee. Although a well-known medical centre, particularly in the field of transplantation, there was no other reason why Harvard should have been the birthplace of such seminal guidelines. The ad hoc committee was formed in response to an internal request, and not under the mandate of any outside and higher authority. The committee was formed within one month of the world’s first heart transplant, completed its work within six months, and the report was published two months later.

Two reasons were given for the redefinition of death in the introduction to the report. First, ‘The burden [of irreversible coma] is great on patients who suffer permanent loss of intellect, on their families, on the hospitals, and on those in need of hospital beds already occupied by these comatose patients.’ Second, ‘Obsolete criteria for the definition of death can lead to controversy in obtaining organs for transplantation.’ Despite this wording, Giacomini argues that transplantation needs were seen by the committee as the main reason to redefine death, but were ‘toned down’ in the final report: ‘transplantation was central to the purpose but detrimental to the rhetoric of redefining death.’

On the one hand, the numbers of patients with irreversible coma, or the ethical and financial issues in continuing their treatment, were probably not seen as significant problems by doctors or the public before 1968. Neither were these issues a prominent topic of discussion by the committee during the report’s preparation. On the other hand, organ donation did seem to be an important issue considered by the committee. However, in the final report, apart from the introductory reference, any discussion of the relevance of brain death to organ transplantation was notable by its absence!

In fact, the Harvard report was followed directly in the same journal by a report entitled ‘Ethical Guidelines for Organ Transplantation’ (American Medical Association, 1968). However, this report did not contain any direct reference to brain death, stating only that (before a vital, single-organ transplant): ‘Death shall be determined by the clinical judgement of the physician . . . (using) . . . all available, currently accepted, scientific tests.’

The controversy about the redefinition of death, even among the committee’s members, is evident from the drafts of the committee’s report. According to Giacomini, one member edited the manuscripts to change every instance of ‘brain death’ to ‘irreversible coma,’ whereas another member (a transplant surgeon) substituted ‘death’ for ‘irreversible coma’!

### Development of the brain death concept

After 1968, various other bodies produced similar guidelines. Mohandas and Chou (1971) described the brain death criteria in use at Minnesota (the ‘Minnesota criteria’). They also suggested that irreversible damage to the *brainstem* was the critical feature of brain death, that this could be established reliably by clinical means, and that an isoelectric EEG was not necessary for diagnosis.

The Harvard criteria were stated to apply to those with ‘no discernible central nervous system activity,’ in other words of the brain stem, cortex and the spinal cord. However, it is now understood that spinal reflexes are often evident in patients who clearly fulfil brain death criteria (Mohandas and Chou, 1971; Ivan, 1973).

In 1970, Kansas became the first US state to recognize legally a neurologically based definition of death (Bernat, 1998). In 1981, guidelines were published in the USA by the medical consultants to the President’s Commission (President’s Commission, 1981). By this time, over half of US states had recognized a

neurological definition of death by statute or judicial decisions. The above guidelines proposed that 'an individual with irreversible cessation of all functions of the entire brain, including the brain stem, is dead.' This report led to the Uniform Determination of Death Act, a 'model statute' that has since been adopted by most US states. This act left the diagnostic criteria for brain death to 'accepted medical standards,' allowing scope for modification of such criteria in the light of new medical knowledge.

In the UK, criteria for brainstem death testing were first set out in a statement from the Conference of Medical Royal Colleges and their faculties (1976). This statement described the practicalities of testing in detail. A further statement by the Conference (1979) proposed that brain death should be recognized as death in a legal sense. Most recently, the criteria have been reviewed and reaffirmed by a working group convened by the Royal College of Physicians (1995), and in a code of practice issued by the Department of Health (1998).

## UK brainstem death criteria

The guidelines described in Table 1 are those of the Royal College of Physicians (1995), and the Department of Health (1998). Phrases printed below in bold

type are taken verbatim from the Department of Health guidelines.

As discussed later, the conceptual definition used in the UK is one of *brainstem* death. It is suggested that 'death entails the irreversible loss of those essential characteristics which are necessary to the existence of a living person. Thus, it is recommended that the definition of *death* should be regarded as *irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe*' (italics added). Death of the brainstem is sufficient to produce this condition. Therefore the tests used are clinical, and (unlike in some countries) there is no requirement to use confirmatory investigations such as EEG or cerebral angiography.

The same criteria are used in children as in adults, although it is recommended that testing is not considered below the age of two months (British Paediatric Association, 1991).

### Timing

Unlike in many other countries, no minimum period is recommended after the onset of coma before testing can take place. It may be rapidly obvious following head trauma that brainstem death has occurred, but longer is needed to predict outcome after cerebral hypoxic damage. For example, Bolton *et al.* (1976) described a patient with absent brainstem reflexes 12

**Table 1** UK criteria for diagnosis of brainstem death (Department of Health, 1998)

1. Preconditions	• The patient is unconscious and apnoeic, due to irreversible brain damage of known cause
2. Exclusions	<ul style="list-style-type: none"> <li>• Hypothermia</li> <li>• Drug effects               <ul style="list-style-type: none"> <li>– CNS depressants</li> <li>– neuromuscular blockers</li> </ul> </li> <li>• Electrolyte abnormalities</li> <li>• Metabolic disturbances</li> <li>• Circulatory disturbances (untreated shock)</li> </ul>
3. Brainstem tests	<ul style="list-style-type: none"> <li>• Pupils fixed and unresponsive to light</li> <li>• Absent corneal reflexes</li> <li>• Absent vestibuloocular reflexes</li> <li>• No motor responses within the cranial nerve distribution to painful stimuli</li> <li>• No gag reflex, or response to tracheal suction</li> <li>• No respiratory movements during ventilator disconnection, when <math>p\text{CO}_2 \geq 6.65 \text{ kPa}</math>. (<math>\text{O}_2</math> given via tracheal catheter at 6L/min to prevent hypoxia)</li> </ul>

#### Personnel and timing

- Brainstem death must be diagnosed by two doctors.
- Both doctors must have been fully registered for  $\geq 5$  years, and at least one should be a consultant.
- Two sets of brainstem tests must be performed. The doctors may perform these separately or together.
- The period between onset of coma and testing, and the interval between tests, are left to clinical judgement.

hours after a cerebral hypoxic episode, who recovered completely within a week. The interval used must be long enough to satisfy the preconditions and exclusions below.

### Preconditions and exclusions

Before the clinical brainstem tests are even considered, the following preconditions and exclusions *must* be satisfied:

1. **There should be no doubt that the patient's condition is due to irremediable brain damage of known aetiology.**

The original wording 'irremediable *structural* brain damage' used by the Conference of Medical Royal Colleges (1976) has been modified. This reflects the fact that damage may (at least initially) be 'micro-structural,' and not always obvious from a CT scan. In cases of head trauma or cerebral haemorrhage, there is usually little doubt about the cause of unconsciousness. However, the diagnosis of hypoxic brain damage rests on circumstantial evidence, coupled with the exclusion of other causes of coma, and observation for a period sufficient to exclude recovery. The principle remains that irreversible *damage* rather than dysfunction must have been diagnosed, either clinically or radiologically.

2. **The patient is deeply unconscious.**

In particular, the following causes of coma must be excluded:

- **Depressant drugs.** This includes *sedative, anaesthetic or any other drugs* that may cause cerebral depression. *Neuromuscular blocking drugs* ('muscle relaxants') must also be considered. A careful drug history must be taken, to include the periods both before and after admission (bearing in mind that drugs given in emergencies do not always appear on the prescription chart!) Traumatic or hypoxic brain damage may occur after drug abuse, in which case persistent drug effects are easily overlooked.

No firm guidelines are available to help exclude residual drug effects, and clinicians must use their judgement: every situation is different. Elimination of drugs may be greatly prolonged in the critically ill, and in hypothermic patients. Wijdicks (2001) suggests that, when concentrations of a drug or toxin cannot be measured, the patient should be observed for at least four times the elimination half-life of the substance – provided that elimination is not delayed by other

drugs or organ dysfunction. If there is any doubt about persisting effects of opiates or benzodiazepines, the respective antagonists naloxone and flumazenil may be used in adequate dosage. The effects of neuromuscular blocking drugs can be excluded by testing for tendon reflexes, or by using a peripheral nerve stimulator.

- **Primary hypothermia.** No definition of hypothermia is given in the *current* UK guidelines, although the 'textbook' minimum of 35°C (as given in the 1976 criteria) is usually used in practice. Brainstem death results in impairment of thermoregulation, which may itself lead to hypothermia; however, this should be corrected by artificial warming before testing is performed.
  - **Potentially reversible circulatory, metabolic and endocrine disturbances.** Electrolyte and blood sugar disturbances are the most likely abnormalities, and may be caused by brainstem death itself (for example, hypernatraemia due to diabetes insipidus). Again, 'required ranges' of electrolyte concentrations are not defined. Electrolytes need not therefore be exactly within the normal range, provided the clinicians concerned are satisfied that any derangement is not contributing towards coma.
3. **The patient is being maintained on the ventilator because spontaneous respiration has been inadequate or ceased altogether.**

Although this may seem self-evident, it is worth restating: any patient who is not on a ventilator is not brain dead! Unfortunately the wording of this statement may lead to confusion, as any genuine respiratory effort is incompatible with a diagnosis of brainstem death. Spontaneous respiration may have been 'inadequate' at presentation, but must be entirely absent before testing can be considered. However, 'respiratory-like' movements can occur, and are discussed later.

When considering preconditions and exclusions, it should be noted that fits, decerebrate or decorticate movements are inconsistent with the diagnosis of brainstem death, as they imply communication between the spinal cord and the brain. However, complex spinal movements can occur in brain or brainstem death, and may in some cases mimic decerebrate movements (see below).

Testing for oculocephalic reflexes ('dolls-eye movements') is *not* included in the UK criteria. However, this is a quick and useful exclusion test, since the

presence of these reflexes excludes a diagnosis of brainstem death. With the tracheal tube temporarily disconnected, and assuming no cervical injury, the head is turned quickly from the mid-position to 90° on each side. The eyelids are held open while this is done, and the eyes are observed for movement, for a few seconds in each position. In brainstem death, the eyes will remain fixed in relation to the head. Any fixation of the eyes on an external object (i.e., the eyes rotate away from the direction of head movement) as the head rotates implies brainstem function. The neck can also be flexed to exclude vertical eye movements.

### Brain stem tests

1. **The pupils are fixed and do not respond to sharp changes in the intensity of incident light.**

Note that the pupils need *not* be dilated, but merely unresponsive to light. Pupils are typically mid-size in brain death, but dilation may occur due to intact cervical sympathetic pathways (Wijdicks, 1995). Confusion may result if eye drops have been used, if high systemic doses of atropine have been given recently, if the patient has a false eye, or if there are other pre-existing eye abnormalities or trauma.

2. **There is no corneal reflex.**

Gentle, then firmer pressure on the outer part of the cornea is applied using a throat swab or similar. Care is needed to avoid damage, if corneal donation is a possibility.

3. **The vestibulo-ocular reflexes are absent.** ('Caloric testing.')

At least 50 mL of ice-cold water is injected slowly (over one minute) into each external auditory meatus in turn. This can be done by using a small suction catheter attached to the syringe, and inserting it carefully into the external auditory canal. No eye movements should be seen either during or after the injection. (Tonic eye deviation towards the irrigated side would normally be expected.) The tympanic membranes must first be inspected with an auroscope to exclude obstruction of the external auditory canals. Although not specified in the UK guidelines, Wijdicks (1995) recommends observing for one minute after irrigation, and an interval of at least five minutes before testing on the opposite side.

No movement should be seen in *either* eye, whichever side is tested, because a lateral rectus

palsy or internuclear ophthalmoplegia may prevent movement on one side. The response may also be abolished by drug-induced vestibular damage, or fracture of the petrous temporal bone.

4. **No motor responses within the cranial nerve distribution can be elicited by adequate stimulation of any somatic area.**

Stimulation can be applied by firm pressure over the supraorbital ridges, or (provided there is no spinal injury) to the nail-beds.

5. **There is no gag reflex or reflex response to bronchial stimulation by suction catheter placed down the trachea.**

6. **No respiratory movements should occur when the patient is disconnected from the mechanical ventilator, and the arterial pCO<sub>2</sub> (measured by blood gas analysis) rises to at least 6.65 kPa.**

The ventilator will usually need to be disconnected for several minutes to allow the pCO<sub>2</sub> to reach this level. To prevent hypoxia during this period, preoxygenation is used (ventilation with 100% oxygen for 10 minutes) before disconnection, and thereafter oxygen is given at 6 L/min through a catheter in the trachea. If equipment allows, the lungs can first be ventilated with 5% CO<sub>2</sub> in oxygen for five minutes, which may itself produce a pCO<sub>2</sub> above 6.65 kPa. Disconnection is then only needed for long enough to observe the absence of respiratory movements.

Although ventilated patients are sometimes hyperventilated, either deliberately or inadvertently, a normal arterial pCO<sub>2</sub> should be aimed for in the hours preceding brainstem death testing. This will facilitate a rise in pCO<sub>2</sub> to the required level. During apnoea, the mean rate of rise of pCO<sub>2</sub> has been reported in various studies to be between 2.4 and 4.0 mmHg/min (0.3–0.5 kPa/min) (Dobb and Weekes, 1995).

Patients with pre-existing chronic lung disease need special consideration, as they may not respond to raised levels of carbon dioxide, and may rely on a 'hypoxic drive' to breathe. The DoH code of practice makes no specific recommendations about apnoea testing in such patients, but simply advises that they should be 'managed in consultation with an expert in respiratory disease.'

### Problems with apnoea testing

The apnoea test is discussed in detail, as it is the most complicated test of brainstem function. Apnoea testing

has often been performed inadequately in the past (Pallis and Harley, 1996). Sedated or neurologically obtunded patients will easily remain apnoeic, if they are ventilated to a normal or low  $p\text{CO}_2$ . Therefore, ventilator disconnection for an arbitrary period without blood gas measurement, or even the definition of apnoea as 'failure to override the ventilator,' are *not* adequate to confirm the absence of central respiratory drive. Apnoea testing without confirming an adequate rise in  $p\text{CO}_2$  has been likened to testing the pupils without a battery in the torch.

The importance of confirming hypercapnia during the apnoea test is underlined by two case reports. Visram and Marshall (1997) report a case in which the arterial  $p\text{CO}_2$  failed to exceed 6.65 kPa even after disconnection from the ventilator for 50 minutes! Oxygen had been supplied via a tracheal suction catheter at 10 L/min during the test. The authors suggest that  $\text{CO}_2$  'washout' may have occurred due to bulk flow of oxygen, together with the 'mixing' effect of the heartbeat. Sharples *et al.* (1997) report that a rise in  $p\text{CO}_2$  may be difficult to achieve in small children, and suggest alternative methods to allow this.

Respiratory-like movements may occur during apnoea testing (Ropper *et al.*, 1981; Urasaki *et al.*, 1992). Such movements include nonrepetitive back arching, shoulder shrugging and cough-like movements, but without effective ventilation. The use of somatosensory and auditory evoked potentials, and autopsy findings, have confirmed that these movements are of spinal origin. Care must be taken to distinguish such reflex movements from genuine respiratory muscle effort, which would preclude a diagnosis of brainstem death.

Apart from the risk of hypoxia, other complications of apnoea testing may occur. Cardiac arrhythmias may arise from hypoxia or hypercarbia (Wijdicks, 1995). Hypotension may be seen due to acidosis if the  $p\text{CO}_2$  becomes very high, and hypertension can also occur, probably from a spinal vasoconstrictor response to hypercarbia (Dobb and Weekes, 1995). Tension pneumothorax has also been reported during apnoea testing (Sharples *et al.*, 1997; Bar-Joseph *et al.*, 1998), and may be a particular risk in children. This can occur if the oxygen insufflation catheter is inserted too far into the trachea, or is of too large diameter, causing air trapping in a distal area of the lung. To prevent tension pneumothorax, Bar-Joseph *et al.* recommend that the catheter should be significantly narrower than the internal diameter of the tracheal tube; that it must never be allowed to 'wedge' against any structure, and

that oxygen flows should not exceed 6 L/min (or less in children).

Willatts and Drummond (2000) reported the case of a patient diagnosed as brainstem dead, who appeared to 'breathe' when connected to the ventilator, but not during disconnection. The authors suggest that small fluctuations in airway pressure due to cardiac contractions caused the ventilator to 'trigger' mechanical breaths. Although apnoea was confirmed when the patient was disconnected again from the ventilator, the concern generated in nonmedical staff resulted in the loss of organs for transplantation. Ng and Tan (2001) reported a similar case in which the patient appeared to take a single 'breath,' probably due to the ventilator triggering after reflex head movement.

Vardis and Pollack (1998) report the case of a child with a cerebral tumour, who had suffered cerebral ischaemia during a cardiorespiratory arrest. On brain death testing, all criteria were fulfilled, except for the apnoea test. Respiratory movements with reasonable tidal volumes were seen during this test, but only at an arterial  $p\text{CO}_2$  of 12.1 kPa. On this basis, the authors use an apnoea threshold of 13.3 kPa in their paediatric unit. However, it is unclear from subsequent correspondence how residual effects of opiates and benzodiazepines were definitively excluded (Vardis and Pollack, 2000; Wenck, 2000).

### Incomplete testing

In some circumstances it is not possible to test all the above brainstem reflexes, for example if there is CSF otorrhoea, a false eye, or drug-induced vestibular damage. However, it is suggested that the tests have 'inbuilt redundancy,' and this does not necessarily preclude the diagnosis of brainstem death.

### Personnel and timing

The original 1976 conference statement did *not* specify that brain death testing should necessarily be repeated. The document merely stated that 'it is customary to repeat the tests to ensure that there has been no observer error,' but that in some conditions this would be unnecessary and 'a prognosis of imminent brain death can be accepted as being obvious.' Neither did the 1976 document require the tests to be performed by two doctors, although it did advise that the decision to withdraw support *after the criteria were fulfilled* should be made by two doctors.

The current Department of Health code of practice (1998) requires that testing should be performed by two doctors who have both been registered for five years, at

least one of whom should be a consultant. Both should be 'competent in this field,' and should not be members of the transplant team. Two sets of tests should always be performed, to eliminate the risk of observer error, and the doctors may perform the tests separately or together. The interval required between tests is left to clinical judgement, but 'should be adequate for the reassurance of all those directly concerned.'

#### **After confirmation of brainstem death**

There is no statutory definition of death in the UK: patients are legally dead when diagnosed as such by a doctor, using accepted criteria. However, in England and Northern Ireland, the brainstem criteria have been accepted by the courts as constituting death in individual cases. Therefore, the patient is declared legally dead, and the time of death is given as the time of completion of the *first* set of brainstem tests.

If organ donation is considered, the situation is discussed with the family, primarily to ascertain the patient's wishes about donation (if known). This is often done after the first set of tests. If done sooner, the family may infer that testing is to be performed mainly with organ procurement in mind. If donation is possible, intensive care of the body is continued as described below. Otherwise, ventilation may be discontinued.

During ventilator withdrawal, spinally mediated movements may occur as described below. If the relatives are to be present when disconnection occurs, they should be prepared for this, but even then they may find such movements deeply distressing. Anecdotally, some clinicians 'slip in' a dose of neuromuscular blocking drug before disconnection, to prevent this occurrence. This is *not* unethical or illegal, since death has already been diagnosed.

In trauma cases, permission must be sought from the coroner if organ donation is considered. However, there is no need to notify the coroner in advance about the performance of brainstem tests themselves, or about ventilator disconnection once brainstem death has been diagnosed.

### **Spinal reflexes in the brainstem dead**

Spinal reflexes are well described in patients fulfilling brainstem death criteria (Ivan, 1973). Tendon reflexes, plantar responses, plantar withdrawal and other responses such as the abdominal and cremasteric reflexes may be seen. These are compatible with a

diagnosis of brain death, just as they are compatible with a complete spinal cord injury.

In addition, various other and more complex movements have been noted. These may occur during apnoea testing, after physical stimulation, or even spontaneously (Mandel *et al.*, 1982; Ropper, 1984; Saposnik *et al.*, 2000). Afferent sensory input to the spinal cord, or severe spinal cord hypoperfusion or hypoxia, are thought to stimulate such movements.

Back arching and respiratory-like movements have already been mentioned. Several reports have described complex movements of both upper and lower limbs, which have become known as 'Lazarus's sign' (Heytens *et al.*, 1989; Urasaki *et al.*, 1992). These movements have been variously reported as occurring during apnoea testing (or after permanent ventilator disconnection), or following noxious stimulation. Pronation of the forearms, and flexion or extension of the elbows, wrists and fingers may occur, affecting one or both arms. Such movements have caused it to appear that the patient is grasping with the fingers, reaching for the tracheal tube, or praying. On other occasions the movements have simulated decerebrate posturing, which would (if genuinely decerebrate) be incompatible with brain death (Christie *et al.*, 1996; Marti-Fabregas *et al.*, 2000). In the latter report, the decerebrate-like movements appeared to be triggered by positive-pressure breaths from the ventilator.

Flexion and extension of the knees and ankles may also be seen, as well as 'undulating' toe flexion. Such alternating and rhythmic movements of the lower limbs may resemble stepping or walking movements, which have been reported during the stages of brain herniation, and even after brain death (Hanna and Frank, 1995). Head-turning movements from side to side have also been reported, in response to passive neck movement or stimulation of the upper body (Christie *et al.*, 1996).

On testing for somatosensory evoked potentials (SSEPs) in a patient with complex limb movements following brain death, Urasaki *et al.* (1992) demonstrated absence of the scalp component but preservation of the spinal component, consistent with a spinal origin for such movements.

These reflex movements can clearly cause serious disquiet among relatives, and also among health care staff who may not appreciate their true nature. Sensitive handling is required to deal with this, especially if relatives are to be present during apnoea testing or terminal disconnection.



Spinal reflexes are not confined to movements, but also include cardiovascular responses. These may occur during organ harvesting, and are discussed later.

## Brain death worldwide

The concept of brain death is accepted in many countries, and Wijdicks (2002) was able to obtain brain death criteria for 80 of the United Nations' 189 member states. Clinical tests of brainstem function are similar in most countries, although there are important variations in apnoea testing procedures. There are also differences in the personnel required, the intervals specified before and between tests, the use of confirmatory tests, and in the legal position.

### USA

The current US criteria for adults are described in practice parameters issued by the American Academy of Neurology (1995), and discussed by Wijdicks (1995, 2001). Criteria for children have been published by the American Academy of Pediatrics (1987). The conceptual definition of brain death differs from that in the UK, being described as the 'irreversible loss of function of the brain, including the brainstem.' However, the preconditions, exclusions and clinical tests used are very similar to those in the UK, with the following exceptions:

- The core temperature required before testing can take place *is* defined, and should be 32°C or above. For the apnoea test, however, core temperature should be at least 36.5°C. The reason given for this is that pCO<sub>2</sub> rises slowly at lower temperatures during apnoea. Other than this, and as in the UK, no specific definitions are given for the exclusion of drug intoxication or electrolyte imbalance.
- Absence of the oculocephalic reflex *is* included in the tests.
- A more specific description of a procedure for apnoea testing is given than in the UK criteria. The pCO<sub>2</sub> that must be achieved during the test is 8.0 kPa (or a rise of 2.7 kPa above baseline), in comparison with the UK value of 6.65 kPa.
- Repeated clinical testing after an arbitrary interval of 6 hours is recommended.
- Confirmatory tests such as EEG or cerebral angiography are recommended only for situations where the clinical tests cannot be properly performed. This would include severe facial trauma, pre-existing

pupillary abnormalities, severe pulmonary disease or sleep apnoea with chronic CO<sub>2</sub> retention. Situations in which 'toxic' levels of sedative, neuromuscular blocking or other drugs may be present, are also included in this list. Confirmatory tests are also recommended for children less than one year old.

- US states have differing requirements about the number and speciality of doctors needed to diagnose brain death. Two states allow registered nurses, after physician certification, to make the diagnosis (Wijdicks, 2002).
- The state laws of New Jersey and New York contain exemptions for those who do not accept the brain death concept on religious or other grounds. These exemptions are discussed later.

### Europe

The situation in Europe has been reviewed by Matesanz (1998), Haupt and Rudolf (1999) and Wijdicks (2002). In almost all European countries, the law accepts brain death as equivalent to death of the person. There are differences in the number of physicians needed to make the diagnosis, ranging from only one (e.g., in Finland, Poland and The Netherlands) to three (as in Belgium and Greece) and even four (in Turkey). Some countries also specify that these physicians should be from particular specialities, such as neurology or neurosurgery. Clinical brainstem tests are very similar in European countries, but there is significant variation in the apnoea test, with some countries still not requiring hypercapnia to be confirmed by blood gas analysis. Most countries specify an interval after the onset of coma before testing can take place, and the time that must elapse before repeated testing (when required).

Confirmatory tests are mandatory in some countries (e.g., France, Italy and The Netherlands), but optional in others (e.g., Austria, Belgium, Denmark, Germany and Switzerland). The required confirmatory tests also vary: most countries accept EEG and cerebral angiography, and some also accept evoked potentials, Doppler sonography and radioisotope scintigraphy. A confirmatory test can be used in some countries as alternative to a repeat clinical test.

### Other countries

Outside Europe and the US, relevant guidelines or laws are prevalent in the countries of South America, the Middle East, Asia and Australasia, but much less so in African nations (Wijdicks, 2002). Mainland China has

no brain death law or guidelines. As in Europe, there are variations in the number and speciality of the certifying doctors, in the intervals required before and between tests, and in the need for confirmatory tests. There are also variations in the apnoea test procedure, with many countries not requiring the measurement of arterial pCO<sub>2</sub>.

The situation in Japan is unusual. Beating-heart organ donation has been delayed for many years, due to a lack of acceptance that brain death constitutes death in a legal sense (Miller and Hagihara, 1997). The surgeon who performed the first Japanese heart transplant in 1968 was investigated for 'murdering' the donor, and even though he was not convicted, the long court case effectively put a stop to such operations for many years. Kidney and partial liver transplants were performed, but were only permitted from live donors. However, a law was finally passed in 1997 allowing organ harvesting from brain-dead patients. Interestingly, this allows the legal recognition of brain death *only* for potential organ donors. Cardiorespiratory criteria must still be used to diagnose death in other patients, although the brain-dead state allows relatives to request withdrawal of active treatment (Bruno and Kimura, 2002).

## The somatic disintegration hypothesis

It is often stated that, after the diagnosis of brain death, cardiorespiratory death always occurs within a very short time despite continued intensive care. This has been called the 'somatic disintegration hypothesis,' and has sometimes been cited to justify acceptance of the brain death concept. The hypothesis supposes that the brain is the 'central integrator' or 'critical organ' of the body, and its permanent loss of function is incompatible with bodily survival. This view is increasingly challenged, as there are several reports of survival for significant periods.

Iwai *et al.* (1989) were able to maintain 'survival' for a mean of 17 days in brain-dead patients treated with both adrenaline and vasopressin: somatic death in all patients occurred *after* treatment was withdrawn. Parisi *et al.* (1982) described somatic survival for 68 days after diagnosis of brain death, until support was withdrawn. (Although initial testing may have been slightly premature because of possible drug effects, post-mortem findings leave little doubt about the diagnosis.) Two case reports describe the

maintenance of brain dead pregnant females for 63 and 107 days after diagnosis, respectively, to allow the fetus to reach sufficient maturity for delivery (Field *et al.*, 1988; Bernstein *et al.*, 1989). Both cases required cardiovascular, temperature and hormonal support; in both cases healthy babies were delivered; and in both cases ventilation of the mother was discontinued after delivery (presumably 'survival' may have been longer otherwise).

From various sources, Shewmon (1998) identified 175 cases in which supposedly brain-dead patients 'survived' for at least a week after diagnosis. Although the majority of these died within two months (either naturally or after treatment withdrawal), four survived for over one year, and one was still alive (at the time of writing) after 14 years. Shewmon suggests that the inevitable occurrence of asystole soon after brain death may have become a self-fulfilling prophecy. As Cranford (1998) put it in the accompanying editorial, 'even the dead are not terminally ill any more.'

However, the validity of diagnosis in Shewmon's cases has been challenged (Wijdicks and Bernat, 1999; Wijdicks, 2001). The 'denominator' for Shewmon's cases is unknown; information was incomplete for the majority, and only 56 cases were thought to have enough information for meta-analysis. Insufficient information is given even in these cases to judge the reliability of diagnosis, specifically in the exclusion of drug effects and the details of apnoea testing. Shewmon assures us that the diagnoses were made by 'presumably competent physicians.' However, that alone has not ensured adequate testing in the past, particularly in relation to the apnoea test (Pallis and Harley, 1996).

It seems unlikely that all of these cases could have been misdiagnoses. However, if one rejects Shewmon's conclusions, the implication must be that many other misdiagnosed patients have had support discontinued, or have been subjected to organ harvesting. As Shewmon puts it, those who support this view should press for 'a moratorium on transplantation until our profession gets up to diagnostic snuff.'

None of the above is to suggest that attempts *should* be made to preserve somatic survival for as long as possible in such cases. Indeed, these cases only serve to confirm that recovery is *not* possible. However, it is possible that the somatic disintegration hypothesis may be increasingly questioned as intensive care techniques develop. If brain death is to continue to be accepted as legal death, it must be on grounds other than the somatic disintegration hypothesis.

## Physiological changes following brain death

Most cases of brain death result from a catastrophic rise in intracranial pressure leading to 'coning,' or brainstem herniation through the foramen magnum. As this process occurs, ischaemic injury in experimental animals progresses caudally from the cerebrum, through the pons and medulla towards the spinal cord (Power and Van Heerden, 1995). This leads to a phase of autonomic hyperactivity, or 'autonomic storm.' Vagal overactivity may occur initially, with bradycardia, reduced cardiac output and hypotension. Ischaemia of the pons then leads to sympathetic overactivity: both an increase in sympathetic neural outflow and an outpouring of catecholamines from the adrenal medulla occur, with resulting vasoconstriction and hypertension. Ischaemia of the medulla then leads to tachycardia, due to unopposed sympathetic stimulation as the vagal cardiomotor nucleus becomes ischaemic. Following this phase, there is a profound reduction in sympathetic outflow, with inappropriate vasodilation, impairment of autoregulation, and hypotension.

This initial 'autonomic storm' leads to ECG abnormalities, and even structural damage to the myocardium and lungs (Novitzky, 1997; Cooper and Basker, 1999). The increased sympathetic activity causes a sudden increase in myocardial work and oxygen consumption. In animals, cell necrosis is seen in both myocardium (particularly the subendocardial region of the left ventricle) and conducting tissue. Hearts transplanted from brain-dead baboons took several hours to regain good function in the recipient, whereas hearts taken from anaesthetized but otherwise healthy baboons regained function immediately. In the lungs, the increased venous return and left atrial pressure caused by vasoconstriction may cause pulmonary oedema and interstitial haemorrhage.

Hormonal changes also occur. Deficiency of anti-diuretic hormone (ADH) is often evident clinically as diabetes insipidus, which may lead to hypernatraemia if excessive urine losses are not replaced appropriately. Hypokalaemia and hypomagnesaemia may also occur as a result of this diuresis, and for other reasons. In animals, reduced levels of free tri-iodothyronine (T3), thyroxine (T4), cortisol and insulin occur, although human findings are less consistent. In brainstem-dead humans, Howlett *et al.* (1989) found changes comparable with the 'sick euthyroid syndrome' (in which

thyroxine and T3 levels are reduced but levels of TSH are preserved). These authors suggested that some degree of hypothalamic and pituitary function might continue for many hours after the diagnosis of brainstem death. (The pituitary receives some blood flow from hypophyseal arteries, which arise extradurally.) A generalized abnormality of cellular function has been described, due to reduced mitochondrial function and intracellular energy production, probably as a result of this deficiency of T3. Hyperglycaemia occurs, due partly to peripheral insulin resistance.

### Management of the brain-dead organ donor

If organ donation is a possibility after the diagnosis of brain death, ventilation and intensive care of the potential donor must continue with the aim of preserving organ function. This subject has been reviewed by Robertson and Cook (1990), and Scheinkestel *et al.* (1995).

The cardiovascular and metabolic changes described above are deleterious to organ function, particularly in the lungs, heart and kidneys. The liver appears to be more resistant to hypotension, with a greater physiological reserve. Changes in the heart and lungs may compound dysfunction in other organs because of inadequate perfusion or oxygenation. If these organs are to be transplanted, their subsequent function in the recipient is in jeopardy.

Many of the disturbances mentioned, such as hypovolaemia, hypothermia or electrolyte imbalance, must be corrected before brain death can be diagnosed. However these complications are likely to recur. With the passage of time the likelihood of complications developing in the donor increases, therefore organ procurement should not be delayed (Scheinkestel *et al.*, 1995).

### Cardiovascular

Hypotension is extremely common in the brain dead, due to the vasodilation and myocardial dysfunction mentioned above. Hypovolaemia is often present, arising from various causes. Dehydration may be due to diabetes insipidus, previous fluid restriction or diuretic treatment for cerebral oedema, or third space fluid losses. Ongoing bleeding may also occur, and hypothermia may contribute to myocardial depression. Fluid replacement and inotropic therapy are important in the treatment of these problems. Vasopressin has been shown to be particularly effective in maintaining cardiovascular and renal function in brain-dead humans, in combination with adrenaline

(Iwai *et al.*, 1989; Scheinkestel *et al.*, 1995). Therapy may be guided by central venous pressure monitoring, and by the use of a pulmonary artery (Swan-Ganz) catheter or oesophageal Doppler monitor. The cardiac arrhythmias reported in brain death are often secondary to biochemical and other derangements, and are treated initially by correcting these causative factors.

### **Respiratory**

Lung injury and pulmonary oedema may be induced by the 'autonomic storm' described above. Other changes may be caused by the presenting condition (e.g., chest trauma), fluid overload, or arise from the patient's dependence on the ventilator (basal lung collapse, consolidation and infection). Treatment includes adequate oxygenation, specific ventilation modes, and positive end-expiratory pressure (PEEP).

### **Renal**

Renal function is at risk chiefly from hypoperfusion, due to hypovolaemia and cardiac dysfunction. Treatment of these problems, as described above, is the mainstay of renal preservation. The use of 'renal protective' drugs such as dopamine and dopexamine is controversial.

### **Endocrine**

Diabetes insipidus is common, and leads to dehydration and hypernatraemia. Excessive diuretic losses can be replaced with hyponatraemic fluid (5% dextrose or 0.45% saline), and minimized by the use of desmopressin (DDAVP). Large volumes of intravenous glucose should be avoided, as they may cause hyperglycaemia. Insulin infusion may be needed to treat the latter problem, although hyperglycaemia in the brain dead is also due to peripheral insulin resistance. Treatment may be needed for other forms of electrolyte imbalance, such as hypokalaemia, hypomagnesaemia, hypophosphataemia and hypocalcaemia, arising from excessive polyuria or other causes.

The generalized defect in cellular function in the brain dead is referred to above. Tri-iodothyronine (T3) administration has been found in some studies to reverse metabolic deterioration, and to improve organ function and haemodynamic stability, although its use is still controversial (Scheinkestel *et al.*, 1995; Cooper and Basker, 1999). The Intensive Care Society (1999) suggests T3 therapy in patients with severe cardiovascular instability, high inotrope requirements and worsening acidosis.

Research by Howlett *et al.* (1989) suggests that cortisol deficiency may *not* be usual in human brain-stem dead patients, although a *relative* cortisol deficiency may be present. Steroid replacement is therefore controversial, but has been advocated by some (Scheinkestel *et al.*, 1995).

### **Coagulation**

As brain death develops, a hypercoagulable state may occur. However, subsequent coagulopathy may ensue, at least partly due to the release into the circulation of tissue fibrinolytic agents from the ischaemic or necrotic brain (Robertson and Cook, 1990). Clotting factors and platelets should be transfused to correct this.

### **Thermoregulation**

The brain-dead patient is often said to become poikilothermic. Metabolic rate is depressed, and vasoconstriction and shivering do not occur in response to hypothermia. The situation may be aggravated if large volumes of room-temperature fluid are given to treat hypovolaemia or polyuria. Significant hypothermia depresses organ function (particularly myocardial contractility), causes cardiac arrhythmias, and worsens coagulopathy. It also leads to a leftward shift of the oxygen dissociation curve, which impairs tissue oxygen delivery. Temperature monitoring is vital, and temperature can be maintained by the use of blankets, external warming devices and warmed intravenous fluids.

### **The harvesting procedure**

Organ harvesting is carried out by a surgical team in the operating theatre. Supportive care is continued as above during this procedure, and is usually overseen by an anaesthetist. Full physiological monitoring is continued from the intensive care unit. In theory a general anaesthetic is not necessary, although this is controversial (see below). However, neuromuscular blocking drugs are needed to prevent reflex abdominal tightening or other movements, and hypertension is controlled with vasodilating drugs or volatile anaesthetics.

Cardiovascular responses during harvesting have been studied by Wetzal *et al.* (1985), Gramm *et al.* (1992) and Pennefather *et al.* (1993). Initial increases in blood pressure and heart rate are common, associated with a rise in systemic vascular resistance. Although this may be disturbing to the observer, the changes are thought to be due to a spinally mediated vasoconstrictor reflex, or spinally mediated stimulation of the adrenal medulla. The latter mechanism is thought to predominate, as serum concentrations of adrenaline

increase out of proportion to those of noradrenaline. Similar blood pressure changes have been reported in patients with complete spinal cord injuries.

For heart and heart-lung donors, a right-sided central venous and left-arm arterial line should have been placed in advance, as the left subclavian and right innominate vein are clamped early in the procedure (Ghosh *et al.*, 1990). Antibiotics and steroids are often given. Blood transfusion may be needed to preserve donor organs, and four units are typically cross-matched for multiple-organ donors.

## Conditions that may be confused with brain death

Clearly, erroneous brain death diagnoses are possible if the *exclusions* for brain death testing are not satisfied – for example in cases of hypothermia or drug intoxication. Several other conditions, listed below, have the potential to be confused with brain death. However, this should not occur if the *preconditions* for testing are satisfied; in other words that a known cause of irreversible brain damage is present.

### Locked-in syndrome

This syndrome is caused by an infarction of the ventral pons, due to either a primary vascular cause, or secondary to conditions such as tumour or infection (Patterson and Grabois, 1986). Severe motor deficit occurs, due to corticospinal and corticobulbar lesions. Features include quadriplegia, aphonia and lower cranial nerve paralysis, but there is preservation of vertical gaze and upper eyelid movement. Consciousness is preserved, and patients are able to communicate by blinking. EEG activity is either normal or ‘minimally abnormal.’ Some patients may have a ‘partial’ form of the syndrome, in which other movements are preserved – most commonly lateral gaze and facial movement, although some movement in one or more extremities occasionally persists. Sensory findings are variable, as are somatosensory evoked responses. Respiratory problems are common, with many (but not all) patients requiring ventilatory assistance. Mortality from the syndrome is high, and respiratory complications are a major cause of death. Permanent disability is common in survivors, although a virtually full recovery is possible.

### Guillain–Barré syndrome

There are many reports of patients with severe Guillain–Barré syndrome ‘mimicking’ brain death (Coad and Byrne, 1990; Marti-Masso *et al.*, 1993; Vargas *et al.*, 2000). Such patients are likely to have persistent, though abnormal, EEG activity, and amnesia may occur in those recovering from this state. Although fulminant Guillain–Barré syndrome can lead to apparent coma and absent brainstem reflexes, ophthalmoplegia is said to be rare. The characteristic history should help the diagnosis.

### ‘Medulla man’

Wijdicks *et al.* (2001) reported a case of severe traumatic coma, in which brainstem reflexes were absent, except for a weak cough on tracheal suction. However, spontaneous ventilation occurred consistently on repeated apnoea testing. The authors state that medullary dysfunction is a final event in rostral-caudal brainstem herniation, but in less severe cases the medulla may remain spared – a state they referred to as ‘medulla man.’ Such medullary function precludes a diagnosis of brain death, despite the otherwise severe and permanent brain damage. Similar cases were also reported by Ropper *et al.* (1981).

### Demyelinating conditions and cerebral ischaemia

Ringel *et al.* (1988) reported the case of a patient with severe multiple sclerosis who suffered a respiratory arrest with coma and hypotension, due to pulmonary aspiration. Brainstem reflexes were absent between 12 and 48 hours afterwards, although the EEG showed abnormal but persistent activity. After two weeks the patient had recovered to his preadmission neurological status. The authors suggested that demyelinated central nervous system structures may be susceptible to an enhanced but reversible conduction block following such an ischaemic event. Clearly, caution is needed in situations such as this, when apparent ‘brain death’ might be diagnosed following an episode of cerebral hypoxia.

### Brainstem encephalitis

This is a rare neurological condition, characterized by ophthalmoplegia, ataxia and hyporeflexia (Al-Din *et al.*, 1982). Cranial nerve involvement occurs, and may lead to facial and bulbar weakness, although some motor cranial nerves are usually spared. Drowsiness may occur, but coma is unusual, and breathing is not normally affected. The condition usually remits spontaneously. A severe case with apnoea, apparent coma

and absence of brainstem reflexes has been reported (Chandler and Brilli, 1991).

## Controversies related to brain death

### Brainstem death versus 'whole brain' death

From the time of the Harvard report onwards, brain death in the US has been defined conceptually as irreversible loss of function of the entire brain, including the brainstem. However, some brain 'functions' are preserved in many patients declared brain dead according to clinical criteria. According to various studies, significant numbers of brain-dead patients do not develop diabetes insipidus, and therefore have persistence of at least some hypothalamic function (Truog and Fackler, 1992). In addition, persistent cortical activity is shown in some cases by the presence of EEG activity (Grigg *et al.*, 1987; Kaukinen *et al.*, 1995). Persistent brainstem evoked potentials have also been reported (Halevy and Brody, 1993).

This has led to debate about what constitutes 'significant' function. The US President's Commission (1981) report stated that 'the functions of the entire brain that are relevant . . . are those that are clinically ascertainable.' Veatch (1993) suggests that, at that time, there was a 'gentleman's agreement that cellular level functions did not count.' Therefore, EEG activity could be seen as the discharge of 'isolated nests of cells,' and did not constitute 'function.' However, this interpretation of the whole-brain concept is open to criticism. Why, for example, is preservation of water homeostasis by ADH secretion (which is not tested for) a less important function than pupillary responses (which are tested)?

In contrast, the UK has avoided such inconsistency by adopting a conceptual definition of *brainstem* death. The brainstem contains the nuclei of the third to twelfth cranial nerves, the reticular activating system (on which consciousness depends), the vasomotor and respiratory centres, and the descending motor and ascending sensory tracts. It is, therefore, the means by which consciousness is generated, by which the higher brain communicates and is aware of its environment, and by which breathing and circulation are maintained. As currently stated, brainstem death equates to 'irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe' (Royal College of Physicians, 1995). This definition, rather than requiring death of the whole brain, defines death of the brain as a whole,

that is, as a functional unit. The preservation of ADH secretion and EEG activity are compatible with this definition, as they do not reflect brain stem function.

However, the UK definition has also generated controversy. Evans and Hill (1989) doubt that testing of brainstem reflexes is enough to establish that the *entire* brainstem has ceased to function. They suggest that, because some brainstem-dead patients do not have hypotension severe enough to require vasoconstrictors, they may have some persistent vasomotor centre function. They also point to the lack of evidence that hypertensive responses during organ harvesting (described earlier) are indeed due to spinal reflexes, rather than residual brainstem activity.

A central tenet of the UK definition is that death of the brainstem always includes death of the reticular activating system, on which consciousness depends. However, the situation may be more complex, as centres above the brainstem may be involved in the level of arousal (Jones and Vucevic, 1992). If one accepts the doubts of Evans and Hill, one must accept the possibility of 'residual sentience' in the brainstem dead, even if this does not amount to consciousness as we understand it. In the majority of cases, where brainstem death is secondary to severe supratentorial damage, this would not seem possible. However, where brainstem death is due to primary brainstem disease, this concern is more relevant. This issue is closely related to the controversy about anaesthesia for brainstem-dead organ donors, discussed later.

Returning to the US whole-brain concept, it seems illogical to persist with this definition while relying only on clinical brainstem function tests for diagnosis. Confirmatory tests are not mandatory in the USA, and Wijdicks (2002) suggests that 'maybe we could do away with confirmatory testing altogether.' The exact significance of residual EEG activity is disputed, but its presence (if tested for) would preclude the diagnosis of brain death in the USA! It is significant that the UK definition has now 'softened' to 'the absence of *clinical brain function* . . .' (American Academy of Neurology, 1995), from the 'irreversible cessation of all functions of the entire brain, including the brain stem.'

### The validity of a brain-based definition of death

#### *Two kinds of death?*

As in the Harvard report, it is argued by many that the complete and irreversible loss of brain function is the 'true' definition of death. The President's Commission (1981) proposed that neurological and

cardiorespiratory criteria for death were two means of diagnosing this same condition. Therefore, traditional cardiorespiratory criteria for death are seen simply as an indirect method of diagnosing this state. Capron (2001) suggests that the term brain death be abandoned, as it leads people to suppose there are two kinds of death, and that brain death is not 'real death.'

Although most doctors accept this view, the public has been less easy to convince. In a survey of over 2000 Americans in 1985, less than 50% agreed that 'brain death' should be used as a legal definition of death (Manninen and Evans, 1985). In a Swedish survey (Sanner, 1994), more respondents would accept autopsy than agree to organ donation, for themselves or a close relative. Reasons given for refusal (for both autopsy and donation) included a fear that the subject would not actually be dead, and a distrust of physicians and the health care system.

The possibility of misdiagnosis is a legitimate concern. In the UK, a 'Panorama' television programme in 1980 focussed on several patients who had been erroneously declared brain dead in the USA, and subsequently recovered (Anon, 1980; Pallis, 1980). These cases did not invalidate the UK brainstem death criteria, and the BBC was heavily criticized by doctors for showing this programme. However, misdiagnoses had still occurred, and the public was hardly to be reassured that the *criteria* were sound, if doctors were not using them properly.

It is tempting to dismiss dissenting opinions about brain death as due to a lack of understanding, which can be corrected by explanation. However, for the lay person, it may amount simply to a difficulty accepting that someone is dead, when so much of him or her is quite obviously alive! In medical terms, this is reflected in the difficulty in naming the 'brain dead body.' Terms such as 'heart-beating cadaver' (or even just 'cadaver') seem somewhat contrived when the 'body' looks and feels so unlike a cadaver to both the medical and lay person!

Pallis and Harley (1996) suggest that loss of the capacity for consciousness can be seen as 'a reformulation . . . of the older cultural concept of the departure of the conscious soul from the body.' Unfortunately the anatomical location of the 'soul,' and the time when it might leave the body, are impossible to know. (Indeed, those of a nonreligious bent might disagree that there even is a soul!) Anecdotally, some lay people seem to believe that even in cases of brain death, the soul might in some way be 'tied' to the body until cardiorespiratory death occurs.

### *Accommodating dissent*

How much freedom should be allowed for individuals to dissent from the brain death concept? In the US, the states of both New Jersey and New York have allowed 'conscientious objections' to brain death criteria (Beresford, 1999). The New Jersey statute prevents the diagnosis of death according to neurological criteria, if there is reason to believe the patient would have disagreed with such a definition on religious grounds – in which case only cardiorespiratory criteria may be used. (This exclusion does not specifically recognize the religious views of family members, as distinct from those of the patient, although it would presumably be difficult for physicians to override such views.) In New York, a patient's next of kin must be notified before a neurological diagnosis of death is made, and 'reasonable accommodation' must be made to any 'religious or moral objections' on the patient's part. Unlike the New Jersey statute, this does not amount to an absolute right of veto by relatives representing the patient's views, and in such a test case, the withdrawal of ventilation was permitted despite relatives' objections (Beresford, 1999).

In the UK, Swinburn *et al.* (1999) describe the case of a patient for whom, despite the diagnosis of brainstem death, the family refused to allow ventilation to be terminated. The family were even able (via a lawyer) to threaten the hospital with a court injunction to prevent this being done. Interestingly, the hospital's legal advisers and a medical defence union both advised the doctors *not* to discontinue ventilation. In the event, the situation was resolved by discussion, and the family agreed to the termination of ventilation after 48 hours. Thankfully, such cases are rare.

### *Do we still need the brain death concept?*

It is sometimes suggested that there is now no need for a neurological definition of death, other than to allow organ harvesting. This is probably true, in that withdrawal of ventilation in critical illness is now widely accepted where the prognosis is very poor (Truog *et al.*, 2001; Way *et al.*, 2002). Guidance from organizations such as the British Medical Association and UK General Medical Council state that doctors have no obligation to continue 'futile' medical treatment, and 'medical treatment' is widely accepted as including artificial ventilation (Intensive Care Society, 2003). The 'abruptness' with which ventilation should be withdrawn is debatable, with some clinicians favouring 'terminal extubation' and others preferring a slower 'terminal weaning' (Truog *et al.*, 2001). However,

given that someone with permanent loss of brainstem function will never breathe again, a sudden discontinuation of ventilation would be the only option. This should, therefore, be acceptable even without the prior diagnosis of 'death.' This was not so in the late 1960s and 1970s, and the brain death concept was developed partly 'to provide a greater degree of legal protection to those involved' in stopping ventilation (Harvard, 1968).

Ultimately, the belief that 'brain death equals death' is a philosophical viewpoint rather than a medical fact. Some medical authors now support a return to cardiorespiratory criteria for diagnosing death (Taylor, 1997; Kerridge *et al.*, 2002), while preserving 'brain death' as a 'social construct' for the purposes of organ donation.

### Religious views

Religious views on brain death and organ donation have been reviewed by Elliot (1999). Although no major world religion prohibits organ donation or transplantation, the concept of brain death is not universally accepted. It is difficult to make generalizations, as there are differences of opinion within individual religions. For example, although the Academy of Islamic Jurisprudence acknowledged the concept of brain death in 1986, it has not been widely accepted because there is no exact definition of death in the *Quran* (Al-Mousawi *et al.*, 1997). Similar differences exist in Judaism (Mayer, 1997). Therefore, when dealing with individual patients and their families, it is wise to avoid preconceived ideas about their likely religious views.

### The 'higher brain' definition of death

The 'whole-brain' definition of death has been criticized, not only by those supporting the concept of brainstem death, but also by those supporting a 'higher-brain' definition. According to this view, permanent loss of consciousness *alone* should be a sufficient definition of death, regardless of the presence of respiration, brainstem reflexes and other vegetative functions (Truog and Fackler, 1992; Veatch, 1993). Such a higher-brain definition was one of the options considered by the US President's Commission in 1981, but no agreement could be reached about what parts of the brain were required for consciousness, and whether the loss of function of such areas could be diagnosed with enough certainty (Halevy and Brody, 1993).

This difficulty is exemplified by guidelines published by the American Medical Association

(1995) recommending that anencephalic neonates could be used as heart-beating organ donors, subject to certain conditions. This guidance was soon retracted (Plows, 1996). The letter of retraction cited the AMA council's concern 'about certain diagnoses of anencephaly and understanding of consciousness in these neonates,' and called for investigation 'of the true state of consciousness in anencephalics so that a better understanding of this condition can be achieved . . .'

Another criticism of the higher-brain definition is the 'slippery slope' argument. The concern here is that such a definition might pave the way not only for patients in the persistent vegetative state (PVS) to be declared 'dead,' but also patients with other conditions such as dementia, in which 'loss of personhood' might be suggested. Indeed, Hoffenberg *et al.* (1997) suggested that organs from PVS patients could be removed *after* their death was hastened by lethal injection. In an American survey (Payne *et al.*, 1996), around 50% of physicians questioned thought that patients in PVS should be considered dead, and 65% believed that (after a *decision* to withdraw therapy) their organs could be used for transplantation.

However, Veatch (1993) argues that by the 'slippery slope' argument, the whole-brain definition is actually less defensible than the higher-brain one: 'those who exclude 'nests of cells' in the brain as insignificant have abandoned the whole brain position and are already sliding along the slippery slope!' According to the higher-brain concept, such arguments would be avoided if permanent loss of consciousness was adopted as the sole criterion for death.

Although the higher-brain definition has been debated for some 30 years, it has 'gone nowhere outside of scholarly journal pages and college seminar rooms,' and no country has seriously considered adopting the concept (Bernat, 1998). To accept this definition would imply a willingness to bury, cremate or remove organs from patients who are still breathing. As Pallis (1995) puts it, 'It would be easier . . . for a professor of philosophy to float such a proposition in front of a group of interested students, than for a clinician to propound it to a group of distressed relatives.'

### Anaesthesia for brain-dead organ donors?

In the UK, a long-standing controversy recently surfaced in the medical and lay press. Guidelines published by the Intensive Care Society (1999) stated that, for the 'operation' of organ harvesting, brainstem dead patients do not require analgesia or sedation. Neuromuscular blocking drugs are, however, given to



prevent reflex movement in response to the surgical stimulus, and hypertension induced by surgery is controlled either with a specific vasodilating drug, or by a volatile anaesthetic agent (which itself causes vasodilation).

A subsequent editorial in the journal *Anaesthesia* (Young and Matta, 2000) criticized this view, and recommended that sedation and analgesia, or general anaesthesia, should always be given. Debate followed subsequently in the same journal, and the controversy also surfaced in the lay press (*The Guardian*, 19 August 2000).

It hardly seems likely that a brain-dead patient could experience consciousness as we understand it. However, those who recommend general anaesthesia would presumably be concerned about the possibility of some residual perception of 'painful' stimuli during the process of organ harvesting.

In practice, at least some anaesthetists act irrationally in this situation. Even the author of the Intensive Care Society's guidelines subsequently admitted to using general anaesthesia for organ harvesting (*The Guardian*, 19 August 2000)! It seems likely that he, and many other anaesthetists, feel 'more comfortable' in so doing, even if they agree on a rational level that consciousness in these 'patients' is impossible. Even Pallis and Harley (1996), strong advocates of the brainstem death concept, recommend the use of general anaesthesia, partly to allay any fears of 'residual sentience' in other observers.

Anaesthetists are familiar with the concept of brainstem death, as well as its hopeless prognosis. Presumably, many are able to reconcile this concept with a desire to give anaesthesia to prevent possible 'residual sentience,' however unlikely this may be. Whether the public would feel so comfortable with this concept is another matter!

### Elective ventilation

To help overcome the shortage of donor organs for transplantation, the practice of 'elective ventilation' was adopted in Exeter, UK, in 1988 (Feest *et al.*, 1990). This involved the identification of patients dying on general wards from cerebrovascular accidents, for whom it was felt intensive care was not appropriate. Such patients would be intubated and ventilated, purely in the expectation that brainstem death would then occur and organ donation would become possible.

Elective ventilation was advocated by some (Williams, 1993; Riad *et al.*, 1995), and was indeed

shown to improve the availability of donor organs. However, the practice could not be justified as being in the best interests of the patients involved, and was subsequently declared unlawful in the UK (Riad *et al.*, 1995). A major concern was the possibility that such patients, after ventilation was started, would *not* progress to brainstem death, but would survive in a permanent vegetative state or similar.

## Conclusion

After well over 30 years, the concept of brain death has become widely accepted throughout the world as signifying death of the person. Conceptual definitions vary, however, with most countries accepting the US' whole-brain definition, and the UK adopting the concept of brainstem death. Although *clinical* diagnostic criteria for these two conditions are identical, confirmatory tests such as electroencephalography are relevant only to 'whole-brain death.'

Diagnostic criteria for brain death vary between countries, and it is possible that greater standardization will be achieved in the future.

Despite its widespread acceptance, some medical and lay people still have reservations about the concept of brain death. It seems unlikely that these controversies will be easily resolved.

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