Occasional Review

Brain death in three neurosurgical units

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Abstract

The validity of clinical criteria for diagnosing brain death has been investigated in three ways. A total of 447 published cases were reviewed. In three neurosurgical units (Cambridge, Glasgow, and Swansea) 609 patients diagnosed clinically as brain dead were studied; 326 had final cardiac asystole while still being ventilated, and ventilation was discontinued in the remainder. No patient recovered. The median time in hospital before the heart finally stopped was $3\frac{1}{2}$ - $4\frac{1}{2}$ days, with 30-40 hours on the ventilator. Analysis of prospective data from three countries on patients with severe head injuries showed that not one of 1003 survivors would ever have been suspected of being brain dead even in their worst state soon after injury.

Recovery after supposed brain death has been alleged in patients who were thought to be brain dead but in fact were not and in cases where reflex movements in the limbs were mistaken for signs of life. The safeguards in diagnosing brain death include establishing irreversible structural brain damage, excluding the effects of drugs, and allowing enough time to elapse to establish the diagnosis beyond doubt. The studies reported here show that the clinical criteria used in the United Kingdom

are reliable. There is no need for confirmatory tests such as an electroencephalogram provided that all the conditions for clinical diagnosis have been fulfilled and all the tests carried out.

Introduction

Brain death cannot occur naturally. It is created by doctors out of therapeutic technology. Many patients who would previously have died rapidly can now have their cardiopulmonary function supported for many hours or days. Some of these resuscitated patients recover completely, which is why these techniques are justified; others are left with varying degrees of disability; a few remain for hours or days in irrecoverable apnoeic coma before their hearts stop—they are brain dead.

The concept of brain death has been largely accepted for several years, not only by doctors but also by lawyers and theologians, many of whom have advised committees in various countries.^{1 2} The concept also seems to be widely accepted by society at large, to judge from the experience of clinicians who have had to explain to families what has happened to one of their relatives. In some places brain death has been recognised by statute as one of the grounds on which a doctor may certify death.³ Such statutes have avoided defining the specific means by which brain death is to be diagnosed, because it is recognised that as experience accumulates and new techniques are acquired criteria may change.⁴ In fact there have been only minor modifications since the first formal criteria were published in 1968 by the Ad Hoc Committee of the Harvard Medical School.⁵ There are now more than 30 published sets of criteria,⁶ and many more are in use in individual institutions. All share a common core, made up of four parts: (a) the establishment of irremediable structural brain damage; (b) the exclusion of reversible causes of unresponsiveness; (c) the demonstration of absence of brain-stem function by clinical tests; and (d) confirmatory investigations.

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The only important disparity between sets of criteria is in the importance ascribed to confirmatory tests such as laboratory investigations of brain function or circulation. Lack of activity on the electroencephalogram (EEG) was included in most early definitions of brain death, although it was soon recognised that there were circumstances when brain death was obvious on clinical grounds alone. It then became clear that an EEG could fail to distinguish clinical unresponsiveness due to depressant drugs from that due to structural damage; that a flat EEG occasionally develops only some time after all the clinical signs of brain death; and that a flat EEG, even when due to structural brain disease, was compatible with survival. Reactions to this were of two kinds. One was to seek for alternative instrumental tests that might be more reliable than EEG, such as angiography, isotope passage or clearance, the measurement of cerebral arteriovenous oxygen differences, or the recording of auditory or somato-sensory evoked responses. The other reaction was to specify increasingly stringently the circumstances in which carefully defined clinical tests would be reliable without the need for confirmatory tests. This was the purpose of the statement published in 1976 by the Conference of Royal Colleges and Faculties of the United Kingdom, entitled "Diagnosis of Brain Death"⁷⁷ (referred to here as the statement or criteria of the UK colleges).

The validity of such clinical criteria can be confirmed in two ways. One is to find out what happens to patients whose ventilatory support is continued after brain death has been diagnosed clinically. The other is to analyse the early clinical features of patients who have survived a period of deep coma to find out whether, when they were at their worst, any of them might ever have been diagnosed brain dead. We present here evidence of the first kind from three British neurosurgical units and of the second kind from an international data bank of patients in coma. We have also reviewed the evidence already published by others, which includes some data about the results of laboratory tests in patients who had been diagnosed brain dead clinically.

Published evidence

Few investigations reported in English have set out to record the consequences of continued ventilation of bodies already diagnosed as brain dead, but such information can be extracted from certain papers which were primarily reporting comparisons of clinical and laboratory criteria of brain death. The same details are not available for all cases, which limits possible comparisons.

In 1971 Mohandas and Chou⁸ reported on 25 patients who were fully supported after the diagnosis of brain death on the Minnesota criteria, all of whom had cardiac arrest and then underwent necropsy. An EEG was recorded in nine cases but was isoelectric in only three. This paper emphasised the discrepancies between these recordings and the clinical and pathological findings. Mohandas and Chou concluded that the EEG was not only unnecessary but could be misleading, though they emphasised that the clinical criteria were recommended only for patients with "known irreparable pathology": they could never be applied to comas of unknown origin. This paper is important because it established the reliability of the Minnesota clinical criteria, which had already been in use there since 1967. The criteria were later applied in other published series and had a considerable influence on the UK colleges' statement.

The US Collaborative Study attempted to define criteria of cerebral death by analysing 503 comatose and apnoeic patients from nine centres.⁹ The design of the study was criticised by American colleagues,¹⁰ while Pallis has recently drawn attention to the lack of stringency in defining both unresponsiveness and apnoea in that study.^{11 12} The diagnostic mix of the cases was different from those of all other published studies, with many fewer cases of head injury and spontaneous intracranial haemorrhage. In all, only 243 patients (48%) had irreparable structural lesions, making them eligible for testing by the Minnesota brain death criteria. Only half were in fact found to be brain dead according to these criteria.¹³ All 141 of these clinically brain dead patients had an EEG, which was not flat in 8%. All 141 suffered cardiac arrest, including those whose EEGs still showed residual activity.

The other sizable US study came from the critical care unit in Pittsburgh, where brain death criteria have been used since 1969.¹⁴ Of the 182 patients diagnosed as brain dead clinically, 164 had an isoelectric record on EEG; all subsequently suffered cardiac arrest, as did the 18 who had persisting EEG activity. The conclusion was that the prognosis was equally hopeless whether or not a clinical diagnosis of brain death was supported by a flat EEG.

There are several smaller series that also document the reliability of clinical criteria. In California all of 15 cases satisfying the clinical components of the Harvard criteria proceeded to cardiac arrest despite the maintenance of "maximum cardiorespiratory support."¹⁵ In Israel 42 patients who were diagnosed clinically brain dead also underwent various laboratory tests, including an EEG in 32, which showed a flat record in all cases. All 42 patients suffered cardiac arrest while still fully supported.¹⁶ In Kenya another 30 cases were given full therapeutic support after the diagnosis of brain death by clinical criteria, and all had cardiac arrest; 10 had an EEG, which was flat in only three.¹⁷ Of 37 clinically brain dead patients in Finland 12 had their ventilatory support maintained and all had cardiac arrest; only four had an EEG.¹⁸

Together these reports record 447 patients diagnosed brain dead by clinical criteria, some of whom still had some activity on the EEG, but all of whom had a cardiac arrest within a few days of this diagnosis. Most of these patients continued on ventilatory support until the heart stopped spontaneously.

Experience in British neurosurgical units

We report three series of brain dead patients, from Glasgow, Cambridge, and Swansea. When taken together these are representative of most British units. One serves a large metropolitan area, another a largely country region, and the third a mixed population. Two are in teaching hospitals, and the numbers of consultants and of junior staff training in neurosurgery are different in the three centres. As in all regional units in Britain, most patients are referred by other hospital specialists, and there is a reluctance to transfer, particularly over long distances, patients unlikely to benefit from neurosurgical intervention because they have overwhelming brain damage.

METHODS

Practice in regard to brain death has developed independently in different neurosurgical units in Britain. We first met to compare our retrospectively reviewed experience in November 1980, in response to the current debate on brain death.

The *Glasgow* unit serves a population of 2.7 million, two-thirds of whom are in the central conurbation. It is situated in one of five general teaching hospitals in the city, in a separate building, which has its own intensive care unit. Head injuries are a special interest, and the collection of prospective data about these cases began in 1968. The Minnesota code was formally adopted for diagnosing brain death in 1972. When the UK colleges' statement was published⁷ the unit adopted its precise specifications for the apnoea test. When the code of practice¹⁹ was published it adopted its model check list for diagnosing brain death as a separate sheet in the case records, in addition to the note made in the normal medical and nursing records.

At *Cambridge* the regional unit for neurological surgery and neurology has one of its wards set aside for the care of patients with head injuries and has access also to beds in the accident wards. It undertakes the primary care of all cases of head injury from the Cambridge district and accepts severe cases of head injury from the rest of East Anglia; the regional population is 2 million. Since its inception (in October 1961) it has maintained the particular interest in head injuries that it inherited from its parent unit in Oxford, and details of some 15 000 patients have now accumulated. As a result of the early Oxford experience, clinical criteria of brain death were formulated locally in 1962, differing only in minor details from the Minnesota code, with the prerequisites that the underlying damage was clear and that everything possible had been done to rectify it.

The *Swansea* neurosurgical department is a non-teaching sub-regional unit. Its catchment area has an industrialised urban littoral, a rural hinterland, and a population of about one million. The unit includes an eight-bedded intensive care ward, which is open to other specialties on request. Nearly all head injuries and most of the cases of spontaneous intracranial haemorrhage are admitted as transfers

from catchment hospitals. Local policy for cases of spontaneous intracranial haemorrhage has been recently stated.²⁰ The UK colleges' criteria were used for diagnosing brain death throughout the period of data collection.

In neither Glasgow nor Cambridge did the neurosurgeons use EEGs for diagnosing brain death, although large EEG services were available in the neurological departments of the same hospitals. While the Swansea neurosurgeons do not regard an EEG as necessary for diagnosing brain death they do find it useful in providing reassurance to relatives, nursing staff, and other doctors.²¹ EEG was used in 70 of the 124 brain dead patients reported here; in three the record was not isoelectric, one proving to be an artefact. In the two other patients the heart stopped while ventilator support was being continued. Inquiry of other neurosurgeons in Britain indicates that most do not use EEGs; those that do so appear to be acting in the spirit of their colleagues in Swansea.

In each unit we scrutinised the original case records of the patients who had been on ventilators during the years chosen for study. Patients who had been ventilated only during terminal resuscitation were excluded; only those established on a ventilator for more than an hour were considered. Obviously patients who were still receiving relaxant or depressant drugs to facilitate their management on a ventilator could not be diagnosed as brain dead by the UK criteria, and these were therefore also excluded. Particular care was taken to record accurately the duration of the patient's stay in hospital before terminal cardiac arrest, and also the time spent continuously on a ventilator before the heart stopped, whether the asystole occurred spontaneously or immediately after discontinuing ventilation.

The availability of records varied in the three units. In Cambridge head injury cases were retrievable from 1962 but other cases only from 1974. In Glasgow information about all deaths (including brain deaths) was reliable only for the last three years. There were therefore variations in the numbers of cases available for different analyses.

Results

The 609 brain dead patients consisted of 130 with head injuries from Cambridge for 1962-74 and 479 cases with various conditions from all three centres in more recent years. Head injury accounted for just over half of the more recent cases, being commonest in Cambridge and least common in Swansea (table I). Only a proportion of patients who die with severe brain damage go through a period of brain death, as defined for this study. This proportion depends on the availability of mechanical ventilation and the policy for its use. The increasing incidence of brain death in cases of fatal head injury in

Cambridge from 1962 to 1980 reflects the progressively greater availability of ventilators and willingness to use them (table II). The increase in the incidence of brain death in Glasgow in the last three years is probably due to changing attitudes towards the role of ventilation in the treatment of severely brain damaged patients, and the much higher rate in Swansea likewise reflects a different view of how to treat these patients.

TABLE III—Incidence of discontinuing ventilation after brain death. Results are numbers of cases in which ventilation was discontinued out of total number of cases of brain death

	Cambridge		Glasgow		Swansea	
	No	%	No	%	No	%
Head injuries:						
1962-9	4/68	6				
1970-5	13/62	21				
1975-7	13/44	30				
1978-80	23/58	40				
All diagnoses:						
1975-7	20/73	27	34/60	57		
1978-80	34/84	40	94/138	68	84/124	68

TABLE IV—Brain dead patients ventilated until spontaneous cardiac asystole

	All patients	Patients with cardiac asystole while on ventilator
Cambridge (head injuries):		
1962-9	68	64
1970-4	62	49
Cambridge (all diagnoses) 1975-80	157	103
Glasgow 1976-80	198	70
Swansea 1978-80	124	40
Total 1975-80	479	213
Grand total	609	326

TABLE V—Duration of stay in hospital before final cardiac asystole in 474 brain dead patients. Results are percentages of patients staying each length of time

Time in hospital	Cambridge 1975-80 (n = 157)	Glasgow 1976-80 (n = 198)	Swansea 1978-80 (n = 120)
< 24 h	17	13	8
1-2 days	17	23	25
2-3 days	10	12	5
3-4 days	8	12	11
4-5 days	4	5	2
> 5 days	44	35	49
Median	4 days	3½ days	4½ days

TABLE I—Primary diagnosis in 479 brain dead patients in neurosurgical units. Results are numbers (percentages) of patients

	No of cases	Head injury	Spontaneous intracranial haemorrhage	Other conditions
Cambridge 1975-80	157	102 (65)	34 (22)	21 (13)
Glasgow 1976-80	198	107 (54)	48 (24)	43 (22)
Swansea 1978-80	124	54 (44)	51 (41)	19 (15)
Total	479	263 (55)	133 (28)	83 (17)

TABLE II—Incidence of brain death in the three centres at different times. Results are numbers of cases of brain death out of total number of deaths

	Head injury		Spontaneous intracranial haemorrhage		All non-traumatic cases	
	No	%	No	%	No	%
Cambridge:						
1962-9	68/193	35				
1970-4	62/152	41				
1975-80	102/209	49				
Glasgow:						
1978	17/57	30	7/36	19		
1979	30/80	38	14/55	25		
1980	33/66	50	15/37	41		
Three centres since 1975:						
Cambridge	102/209	49			55/139	40
Glasgow	80/203	39	36/128	28	139/489	28
Swansea	54/64	80	51/61	84		

What is done once brain death has been diagnosed depends on the circumstances, the clinician, and the patient's family. The confidence to consider withdrawing ventilation was gained only gradually (table III). Over 19 years the proportion of head-injured brain dead patients in Cambridge whose ventilators were electively stopped has increased steadily from 6% to 40%. Ventilation is, however, still discontinued less often in Cambridge than in Glasgow or Swansea, both for head injuries and other kinds of brain damage. In all three places, however, there are still many patients who suffer terminal cardiac arrest while ventilation is being continued. There are several reasons for this. The heart may simply stop before a decision to discontinue ventilation has been reached; the decision may have been deferred because the relatives cannot be reached; or the family, or even sometimes the doctor, may be reluctant to have the ventilator switched off. Whatever the reasons, this has provided a large series of patients who have been maintained with ventilator support after the clinical diagnosis of brain death until their hearts stopped (table IV). These 326 patients (213 since 1975) can be added to the 447 already published by others to support the contention that once the brain is dead then the heart invariably stops also.

The time spent in hospital and the period on the ventilator before the heart finally stopped varied widely, being prolonged in a few cases. The median is therefore the best way of summarising this information, but the distribution of times is given in tables V and VI. The median time in hospital ($3\frac{1}{2}$ – $4\frac{1}{2}$ days) was about three times as long as the time on the ventilator (30–40 hours); hospital stay was more than twice as long in the non-traumatic cases. There was therefore ample time to establish a diagnosis of irreversible brain damage and for the effect of drugs that might be influencing responsiveness to wear off. The few patients that were only briefly in hospital or on the ventilator had brain damage that was so overwhelming that secondary hypotension or spontaneous asystole soon made this obvious.

TABLE VI—Time on ventilator until final cardiac asystole. Results are percentages of patients

Time (h)	Cambridge 1975–80 (n = 157)	Glasgow 1976–80 (n = 198)	Swansea 1978–80 (n = 121)
<6	12	6	4
6–12	12	12	3
13–24	15	22	20
25–48	24	34	35
49–72	13	10	10
>72	24	16	28
Median	32 h	30 h	40 h

Survivors from coma

Prospective collection of detailed clinical data on all patients in coma after severe head injury began in Glasgow in 1968, and it was later extended to include cases from other centres in Britain, the Netherlands, and the USA.²² There are now 1939 patients on this data bank. Only patients in coma for at least six hours were included; all cases were treated with vigour in specialist centres. Although therapeutic techniques differed, with more frequent use of drugs, decompression, and mechanical ventilation in the American centres, the mortality (about 50%) was similar everywhere.²³ Details were available for each patient on motor responsiveness, pupil reactions and eye movements, other injuries, and the exact state of respiratory function; for each of a number of intervals after injury both the best and the worst functional state of the patient had been recorded.

For the present study the clinical data on 1003 patients still alive three months after injury were scrutinised to discover whether there were any who might have appeared to be brain dead in the early stages. Computer analysis indicated that 127 patients had had complete unresponsiveness of the limbs as their worst state at some time during the first week. One hundred and two of these patients, however, had had active eye movements, reactive pupillary reflexes, the capacity to breathe spontaneously, or a combination of the three. To determine whether any of the remaining 25 patients, who were completely unresponsive and had been ventilated, might have been considered to be apnoeic from brain-stem damage the full clinical records of each of these patients were re-examined by the original data collectors in Rotterdam, Los Angeles, San Francisco, Leeds, and Glasgow. In every case there was another, and obvious, reason for their being ventilated: either associated injuries to the chest or trunk or secondary pulmonary complications. These patients were being electively ventilated and were receiving depressant or relaxant drugs, or both. They could not therefore have been considered for tests of brain death because they were not apnoeic from brain damage.

Estimated incidence and distribution of brain death in Britain

The incidence and distribution of brain death nationwide cannot be discovered from any published statistics. Its occurrence in neurosurgical units in Britain can be estimated from our studies, given that policies and practices are largely similar elsewhere. From epidemiological studies of these conditions in this country, the proportion of patients who die of head injury and of spontaneous intracranial haemorrhage in neurosurgical units and in other hospitals can also be estimated.

Each year there are 45 deaths in British hospitals from head injury

per million population.²⁴ If a similar proportion became brain dead as in our three units, there would be 1660 cases of brain death after head injury each year. About a third of deaths in hospital from head injury in the regions of Cambridge and Glasgow occur in the neurosurgical units, which have a special interest in this condition. Elsewhere this proportion is likely to be smaller. According to a study of subarachnoid haemorrhage, in a part of England where the neurosurgeons were particularly anxious to admit cases as soon as possible, just under half the hospital deaths from this condition occurred in the regional neurosurgical units²⁵; in the rest of Britain this proportion is probably about a third. We estimate that about 1200 patients suffer brain death in hospital each year from spontaneous intracranial haemorrhage (most of them subarachnoid haemorrhage from ruptured aneurysm).

Another source of information about the distribution of brain death is from analysis of cadaver renal donors. The primary diagnosis in 1000 donors from the West Midlands in 1968–77 was head injury in 45% and subarachnoid haemorrhage in 45%.²⁶ Preliminary analysis of some 1400 donors notified since January 1978 to the UK Transplant Service indicates that about a third came from neurosurgical units; over half of all donors had a head injury and a third had intracranial haemorrhage. These findings are compatible with the estimates based on extrapolation from our own data.

Discussion

In Britain most cases of brain death result from head injury or spontaneous intracranial haemorrhage. Such obviously badly brain-damaged patients are put on ventilators in the hope that their apnoea will be only temporary. Recovery may occur spontaneously, result from the improved oxygenation associated with restored ventilation, or follow relief of intracranial pressure by medical or surgical means. Many patients with head injury or spontaneous intracranial haemorrhage therefore go to neurosurgical units for investigation, so neurosurgeons became the first specialists to gain a concentrated experience of brain death. In the USA neurosurgeons were in the forefront in formulating criteria of brain death and more recently in reviewing the state of the art.^{3 5 6 8 15 27–30} The diagnosis of brain death is not, however, the prerogative of neurosurgeons, especially in Britain, where probably two-thirds of deaths due to head injury and spontaneous intracranial haemorrhage occur in the beds of other specialists. Doctors in many hospitals and departments therefore need to be able to diagnose brain death with confidence. To facilitate this the UK colleges issued their statement on the diagnosis of brain death in 1976—eight years after the publication of the Harvard criteria⁵ and five years after the classical paper from Minnesota.⁸ With an estimated annual occurrence of more than 2500 cases of brain death in Britain alone, a vast experience had accumulated by this time in many countries, though little had been published.

One characteristic of the British criteria is the detailed specification of the procedure necessary to confirm that the patient is genuinely apnoeic. This includes a long enough period of disconnection to assess whether a damaged, but still viable, brain stem is capable of responding. Preoxygenation and oxygen diffusion during disconnection protect the brain and heart from hypoxia during the period of the test. As the absence of all spontaneous respiratory activity is the cardinal feature of the diagnosis of brain-stem death, it is surprising how inadequately it is tested for in some codes, in particular that of the US Collaborative Study.¹¹

ALLEGED ERRONEOUS DIAGNOSIS OF BRAIN DEATH

The case for confirmatory tests seems to derive from reports of the recovery of patients supposedly diagnosed as brain dead. Such reports are usually in the public rather than the medical press, and there are seldom adequate details to judge the merits of each case. Recorded cases were mostly in the early 1970s, but rumours about others still circulate occasionally. The most recent were the American cases shown in October 1980 on

BBC's *Panorama*.³¹ A year before the UK criteria were published one of us (BJ) had written about the various kinds of alleged error,³² which fall into the following clearly defined and readily recognised categories.

Patients were not brain-stem dead but were thought to be

Absence of signs of brain-stem function—This occurs when there is (a) temporary depression of brain-stem activity by depressant drugs, metabolic disorders (including hypoxia and hypotension), or hypothermia; and (b) absence of muscle function because of muscle-relaxant drugs, causing peripheral paralysis, apnoea, and loss also of spinal reflexes.

Confusion with other types of severe brain damage—The commonest is the *vegetative state*,³³ when the cerebral cortex is rendered functionless either by hypoxia (usually from cardiac arrest) or by widespread disruption of subcortical white matter (after impact injury to the head). Such patients are not sentient and make no psychologically meaningful response, but their brain stem is intact. They may open and move their eyes; have active pupillary, corneal, and pharyngeal reflexes; and are capable of postural and other primitive movements in the limbs. They breathe normally and, if adequately nursed, may live for years in this state. A much rarer state is the *locked-in syndrome*,³⁴ which results from massive destruction of the ventral portion of the brain stem above the medulla (usually from basilar artery occlusion). Although all four limbs are paralysed, the patient is still capable of conjugate vertical gaze and can still breathe. Such patients are conscious and if survival is prolonged they may learn to communicate by code, using their remaining voluntary motor activity—upward movement of the eyes and eyelids. Confusion in the lay mind between brain death and a *bad prognosis* may also lead to the wrong belief that someone is brain dead. Saying that the outlook is almost hopeless and that the patient may die is not the same as diagnosing brain death. But it is understandable that, at a time of crisis and distress, relatives trying to recall what a doctor said may sometimes fail to make this important distinction. Faced with such a prognosis relatives may themselves raise the matter of organ donation, although the doctor would not normally do this until unequivocal brain death had actually occurred. Such patients sometimes recover, at least partially or temporarily. It is incorrect and misleading then to suggest that this occurred after a mistaken diagnosis of brain death or to hint that plans were made to remove organs before the patient was dead.

Patient was brain dead, but was thought not to be

The presence of reflex movements in the limbs, arising from a still-viable spinal cord released from inhibitory influences from above, can readily give the mistaken impression to inexperienced bystanders that the brain is in fact still alive. These reflex movements are apt to return when ventilation is maintained for more than 24 hours after brain death has occurred, and they may be precipitated by the terminal anoxia that follows discontinuation of ventilation. It is important to explain to everyone present that this may occur, before misunderstanding arises.

SAFEGUARDS IN THE CLINICAL DIAGNOSIS OF BRAIN DEATH

Establishment of irreversible structural brain damage

In cases of head injury or spontaneous intracranial haemorrhage brain death may follow the initial incident. The patient is deeply unconscious and flaccid from the outset, and apnoea may develop soon after reaching the first hospital. In most cases the history is clear cut and there are witnesses to the onset of the coma. On the other hand, brain death may be a later event occurring as a complication of the head injury—for

instance, as a result of intracranial haematoma, diffuse brain swelling, fat embolism, or meningitis. In such cases investigations and therapeutic endeavours must be exhaustive before the irreversibility of this secondary brain damage is accepted.

When recurrent subarachnoid haemorrhage occurs in hospital investigations to show the lesion (aneurysm or angioma) may already have been done. Even if they are not complete, the diagnosis is self-evident and the question of drugs can be excluded. Apnoea is common immediately after a major subarachnoid haemorrhage. This may be prolonged for two to three hours and be followed by recovery, provided mechanical ventilation is maintained during this period. Sometimes recurrent haemorrhage occurs during angiography or surgery under anaesthesia, the patient never waking up or breathing again. Or there may be a steady decline, as spreading cerebral ischaemia develops, either after the haemorrhage or after surgery.

Exclusion of hypothermia, metabolic disturbance, and the effects of drugs

There is no difficulty in measuring body temperature or recognising biochemical abnormalities in blood that indicate metabolic imbalance of a degree likely to cause deep coma. These are usually due to hepatic, renal, or respiratory failure or the consequences of a recent period of cardiac arrest. Drugs are more difficult to detect, except for muscle relaxants, the effects of which can be detected by a nerve stimulator. Alcohol is by far the most common drug and complicates about a third of cases of severe head injury when first admitted. A blood concentration of less than 200 mg/100 ml will not cause complete unresponsiveness, even in association with head injury.³⁵ As the blood concentration falls at the rate of 10–15 mg/hour, alcohol is unlikely to exert a major effect more than six hours after injury. Barbiturates and benzodiazepines can readily be detected in blood and have long half-lives. Some less common drugs are more elusive.

If there is the slightest suspicion of intoxication there is no alternative but to wait until the effect must have worn off, or, as is more usual, until the patient's condition worsens as any influence of drugs diminishes, indicating that there must be another cause for the arrested brain-stem function. The distinction between the majority of cases, where the degree of the brain damage is obvious, and the few in whom an element of doubt exists is a feature of the Finnish criteria.¹⁸ The need to consider these possible confusing factors is likewise made clear in the UK statement.⁷

Allowing time to elapse

Time is the best safeguard of all. One of the benefits of formal criteria is that a certain time must inevitably lapse before they can be fulfilled beyond doubt. Certain criteria published many years ago specified intervals between the first and second occasion on which tests for brain death had to be satisfied (varying from 1–24 hours). It is now realised that the more important interval is that which has elapsed since the occurrence of apnoea. Walker has suggested that brain death should not normally be declared in less than six hours after breathing stops, even when a cause of structural damage is obvious.²⁸ It takes this time to allow spontaneous recovery to occur; to correct reversible factors such as hypoxia, hypotension, or cerebral compression; and to carry out any diagnostic tests that are appropriate.⁹

How much longer to wait depends very much on the diagnosis and the circumstances. When the whole event occurs in a patient already in hospital and investigated a confident diagnosis can certainly be reached sooner than when a patient is admitted immediately after a head injury or other event. When the cause of the coma has been cardiac arrest then at least 24 hours should elapse. If drugs are suspected and there are no toxicological

facilities the period of observation may be longer still. In cases where a structural lesion cannot be shown there may be no option but to maintain full support for several days. When in doubt there is no doubt: one should not diagnose brain death.

PLACE OF CONFIRMATORY INVESTIGATIONS

The other distinctive feature of the UK criteria is the explicit statement that confirmatory investigations (in particular the EEG) are not necessary, provided the preconditions have been fulfilled and the clinical criteria have been strictly defined and applied. This was not the first publication to propose that confirmatory laboratory tests are not necessary (while recognising their value in establishing the primary intracranial diagnosis in some cases). A year after the Harvard criteria were published Beecher, a member of the original committee, wrote: "The Committee was unanimous in its belief that an electroencephalogram was not essential to a diagnosis of irreversible coma."³⁶ In a parallel editorial³⁷ Shillito, a Boston neurosurgeon, wrote: "Let us never insist that in *all* cases death cannot be pronounced without electroencephalographic confirmation, for this would take from the physician the value of his competent judgment and relegate it to a machine." Two years later (1971) the case for using only clinical criteria was put forcibly by the neurosurgeons from the University of Minnesota,⁸ and they have recently restated this case.³⁷ In the same year the Finnish National Board of Health published criteria that distinguished between cases where the cause of brain damage was increased intracranial pressure secondary to contusion, haemorrhage, tumour, etc (in which clinical criteria alone were required) and other cases, for which further examinations might be required.^{18 38}

In 1975 editorials in both the *British Medical Journal*³⁹ and the *New Zealand Medical Journal*⁴⁰ drew attention to the reliability of clinical criteria. Noting the colleges' statement, in 1976 the *British Medical Journal* concluded that there was now a consensus of medical opinion throughout the Western world on the diagnosis of brain death. It added, optimistically, "perhaps we may now see an end to uninformed comment on this topic."⁴¹ The *Medical Journal of Australia* echoed this sentiment and welcomed the criteria as an "admirable practical statement from an exceptionally authoritative source."⁴² The *South African Medical Journal* commented that the colleges' statement included nothing particularly new, but that "it does seem to cut through a lot of philosophical and theoretical argument, by bringing the subject back where it belongs, in the hands of the experienced doctor who uses his clinical judgment."⁴³ Sweet, the neurosurgeon on the original Harvard Committee of 1968, commending the UK colleges' statement, went on: "Although I have no quarrel with our British colleagues that (EEG) confirmation is not necessary, I would point out that in the US a climate of general public uneasiness about brain death exists, partly engendered by sensationalised fiction."³⁰ He went on to note that by August 1978 the Inter-Agency Committee in the US (a committee to advise on irreversible coma and brain death, which included representatives from the main US national neurological, neurosurgical, neuropathological, and electroencephalographic societies) had still not been able to agree on the role of the electroencephalogram. The American Neurological Association had in 1977, however, downgraded the EEG from its main list of conditions for the diagnosis of brain death⁴⁴ to "a recommended valuable confirmatory indicator."⁴⁵

Conclusions

The importance of validating clinical criteria for the diagnosis of brain death can hardly be exaggerated. The need for such criteria will remain until a reliable, relevant, and readily available confirmatory test becomes available. The experience that spontaneous cardiac arrest is inevitable once strict criteria of

brain death are fulfilled has until now remained largely personal and unwritten, brought by numerous clinicians to the committee tables of the many hospitals and associations that have formulated criteria over the last 12 years. Few considered their experience sufficiently novel or of enough scientific interest to warrant publication. This is perhaps unfortunate, especially as it has encouraged some who are not familiar with this topic to question whether the reliability of the clinical criteria has ever been adequately tested. Because this diagnosis now often leads to the withdrawal of ventilation some have even alleged that the diagnosis is itself a self-fulfilling prophesy.

We have set out to correct this mistaken impression by reviewing published evidence and our own extensive experience. Many patients in each of our centres have been followed to cardiac arrest while ventilation was maintained, and a substantial proportion still are. There are still some doctors who prefer to wait for spontaneous cardiac arrest, and their views should be respected. On the other hand, families increasingly often ask that ventilation be discontinued once brain death has been declared, and many doctors on both sides of the Atlantic now consider that families should not be allowed to feel that they must carry the burden of this decision; instead they should be brought to realise that, as the patient is already dead, the sensible sequel is to stop ventilation.

It is difficult to imagine that compassionate doctors would be prepared at this late stage to embark on a study that involved deliberately prolonging the mechanical ventilation of patients confidently diagnosed as brain dead when so much evidence is already available attesting to the reliability of this diagnosis. Not only have we ourselves never encountered recovery in a patient fulfilling the UK brain death criteria but, even in the aftermath of the recent public controversy about this issue, we have been told of no cases that were well enough documented to be convincing. There is, however, still a need to ensure that the criteria are widely distributed and brought to the attention of all doctors and nurses dealing with badly brain damaged patients; and that all the conditions are fulfilled and all the tests faithfully applied in every case, and by doctors experienced in the management of patients in coma. The unwarranted anxieties generated by recent misinformed comment on this topic might most effectively be allayed if the appropriate authorities were seen to take steps to ensure that doctors everywhere abided by the recommendations of the Conference of Royal Colleges on the diagnosis of brain death.

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What is a safe cheap antimalarial treatment?

Chloroquine is the best drug for treating acute malaria due to *Plasmodium vivax*, *P. ovale*, or *P. malariae* and most cases of *P. falciparum* in Africa. Primaquine (usually a 14-day course) is given after the chloroquine to reduce the incidence of relapses of *P. vivax*, *P. ovale*, and *P. malariae*. (Opinion differs whether relapses of *P. malariae* occur.) A single dose of chloroquine (for instance, 4 × 150-mg base tablets in adults) may be effective in semi-immune natives. A high proportion of falciparum cases in Asia and Latin America and a small proportion in Africa show partial or total resistance to chloroquine but are cured by sequential treatment with multidose quinine followed by a single dose of pyrimethamine (Fansidar) or mefloquine.¹ Resistance to Fansidar alone is increasing.² Mefloquine is a powerful single-dose antimalarial drug with a long half-life of 14 days.³ It is currently expensive and has not yet been marketed because the WHO fear that resistance to the drug will develop rapidly. Therefore, combined single-dose treatment with mefloquine and Fansidar is being considered to reduce the rate of development of resistance.

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How may dyslexia best be detected in the sufferer?

Developmental dyslexia, or specific reading retardation, may be roughly defined as a specific disability in reading that has arisen in a person of normal intelligence despite adequate teaching and opportunity to learn. The problem may be suspected in young, otherwise bright children, who have a family history of the condition, show language delay, or have difficulties in perceptual tasks. In older children an assessment carried out by an educational psychologist, using standardised tests of intelligence and reading ability, is the only sure way of confirming the diagnosis and should, in any case, be carried out as the best guide to remedial action. Many children suspected of suffering from dyslexia are in fact generally backward. The identification of deficits associated with dyslexia, such as motor clumsiness and difficulties in right-left orientation, is often possible but is of rather limited value in management. Adults who have

suffered from dyslexia in childhood may be identified by the fact that they often remain poor spellers. Some continue to have difficulty in reading and committing thoughts to paper, while others, despite poor spelling, are otherwise verbally fluent.

If the daily weight of stools is related to the daily fibre content of food, how is it that breast-fed babies have any stools at all? What are the constituents of the infant stool? Are they just bacteria and the remnants of gut epithelial cells, or is breast milk incompletely digested?

When a stained smear of the stool from an entirely breast-fed infant is examined microscopically masses of Gram-positive lactobacilli of "bifidus" type may be seen, with a notable absence of any cellular or other organic debris.¹ Thus an entirely breast-fed infant's stool consists of fluid and the lactobacilli in very large numbers. This explains why an infant fed entirely on the breast cannot pass a formed stool.²

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How is hypoglycaemia diagnosed? How valid is the five-hour or six-hour glucose tolerance test?

I assume that the questioner is interested in biochemical confirmation of a clinical suspicion of organic hypoglycaemia. The prolonged glucose tolerance test is now thought to be too insensitive and has been replaced by estimations of the blood glucose concentration after overnight fasting for 12-15 hours or in some clinics fasting for up to 36 hours, in both cases accompanied by mild exercise. Fasting serum insulin concentrations may be raised, and in particular the normal relationships between blood glucose and serum insulin may be reversed.¹ If the diagnosis cannot be confirmed and suspicion remains it may be necessary to carry out provocation tests with alcohol, insulin, or tolbutamide, but these should be done with great care because they may result in dangerous hypoglycaemia.

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