An Appraisal of the Criteria of Cerebral Death

A Summary Statement

A Collaborative Study

- Based on the findings in a collaborative study of 503 comatose and apneic patients, the establishment of cerebral death requires (1) that all appropriate examinations and therapeutic procedures have been performed, (2) that cerebral unresponsivity, apnea, dilated pupils, absent cephalic reflexes, and electrocerebral silence be present for 30 minutes at least six hours after the ictus, and (3) that if one of these standards is met imprecisely or cannot be tested, a confirmatory test be made to demonstrate the absence of cerebral blood flow. This would allow the diagnosis of a dead brain to be made in patients with small amounts of sedative drugs in the blood, in patients undergoing therapeutic procedures that make examination of one or more of the cranial nerves impossible, and in patients otherwise meeting the criteria whose pupils are small.

(JAMA 237:982-986, 1977)

THE STATE generally known as cerebral death, although described more than two decades ago, came to the attention of physicians and the public when transplant surgery gained popularity. The need for viable organs led surgeons to seek patients with intracranial pathological findings such as head injuries that resulted in a dead brain. However, if the pronouncement of death were delayed until the heart stopped beating, the organs underwent so much deterioration that a successful transplant was jeopardized. Hence, a definition of human death that considered the lack of cerebral function as important as the cessation of cardiac activity was recognized. As a result, medical organizations and individuals of many countries proposed definitions of death based on a number of altered states considered to be indicative of cessation of brain function. These include coma, apnea, areflexia, flat EEG, and an absence of cerebral blood flow (CBF). To test the validity of these altered states as indicators of cerebral death and to formulate a set of criteria that would identify a dead brain in an otherwise living body, the National Institutes of Neurological Diseases and Stroke (NINDS; now National Institute of Neurological and Communicative Disorders and Stroke), acting on the advice of an advisory committee, sponsored a collaborative study.

Eight centers geographically distributed throughout the United States initially applied to participate in this program (see p 986). (A ninth was added later.) The study was to be a pilot project for a later definitive program designed to elaborate the findings and to correct defects of the initial project. This pilot study collected data on the clinical findings, the EEGs, the laboratory analyses for drugs, and the neuropathological reports on the dead brains. This data bank is being used for a critical appraisal of the criteria of cerebral death.

Before describing the clinical program, a number of terms commonly used in discussing the subject should be defined.

DEFINITION OF TERMS

In the first place, the distinction between cerebral death and irreversible coma should be clearly understood. Cerebral death implies total destruction of the brain so that both volitional and reflex evidences of responsibility are absent.1-4 Irreversible coma refers to a vegetating state in which all functions attributed to the cerebral cortex are lost but certain vital functions such as respiration, temperature, and blood pressure regulation may be retained.5-8 The practical importance of this distinction lies in the fact that current legal statutes in a number of states recognize cerebral...
**Relationship of Primary Diagnosis to Age**

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*SAH indicates subarachnoid hemorrhage.

death but not irreversible coma as a means of certifying death.

In the second place, certain terms have been used in this study with specific connotations.

Cerebral unresponsiveness (deep coma) denotes a state in which the patient did not respond purposefully to externally applied stimuli, obeyed no commands, and did not phonate spontaneously or in response to a painful stimulus.

Apnea refers to the absence of spontaneous respiration, manifested by the need for controlled ventilation (that is, the patient made no effort to override the respirator) for at least 15 minutes.

Electrocerebral silence (ECS)—isoelectric or flat EEG—denotes an EEG with absence of potentials of cerebral origin over 2μV from symmetrically placed electrode pairs ≥10 cm apart and with interelectrode resistances between 100Ω and 10,000Ω. In exceptional cases, especially if needle electrodes were being used, satisfactory records made with needle electrodes with higher resistances were accepted.

**CLINICAL METHODS**

The pilot study analyzed the clinical data, EEG findings, and laboratory reports of drug analysis on 506 patients suspected of brain death. The table gives the primary diagnosis and age distribution of the cases.

The details of the study have been given in a series of articles and will only be summarized here. In brief, the protocol required that every patient over the age of 1 year admitted to the participating medical center or hospital in a cerebrally unresponsive state and apneic for 15 minutes be entered in the study regardless of the causative agent. Those patients were to have clinical, neurological, and EEG examinations at the time of admission; at 6, 12, and 24 hours thereafter; and then each day for three days; after which, the patient was to be studied semweekly or weekly until death or recovery. If death ensued, autopsies were to be performed when permission could be obtained. The observers did not participate in the diagnostic studies or treatment of the patient who was under the care of the attending physician.

**CRITIQUE OF INDICATORS OF CEREBRAL DEATH**

The validity and limits of reliability of the present criteria of a dead brain may be assessed against the data bank of this study. Both the prerequisites that must be met—absence of sedative drug intoxication, hypothermia, cardiovascular shock, and a remedial primary disorder—and the specific criteria of cerebral death—unresponsiveness, apnea, and ECS—may be evaluated.

**Prerequisites**

Most of the prerequisites relate to reversible conditions that may simulate the usual criteria of cerebral death. Because these disorders may lead to an erroneous diagnosis of a dead brain, their absence is commonly stipulated before the criteria of cerebral death may be applied. However, the practicality of eliminating the presence of these factors may be questioned on the basis of the findings of this study.

Absence of Sedative Drug Intoxication.—In this study, difficulties in eliminating the possibility of drug intoxication arose from the unreliability of the history of drug ingestion, the virtual impossibility of obtaining accurate analyses of toxic agents within a few hours, and the assessment of the significance of minimal amounts of drugs in the blood. Reports of drug levels in the blood were frequently delayed hours or days, and when obtained, these levels were often in the therapeutic range even though the patient was deeply comatose. Moreover, although the protocol required that blood be drawn in every case, half of the patients admitted to the study never had blood analyzed for intoxicants. These difficulties are discussed in detail in another article.

Normothermia.—The determination of hypothermia was more reliable; in the few cases in which it existed in this series, the application of external heat in all but two moribund patients raised the body temperature to normal levels. However, the possibility of error existed in seven cases in which the temperature was not taken.

Absence of Cardiovascular Shock.—In addition to disturbances of thermal regulation when the brain stem and hypothalamic centers are damaged, there may be impairment of vasomotor control, manifested by the clinical picture of shock. This not only depresses CBF severely, but also causes transient suppression of EEG activity, hence the spurious interpretation of cessation of cerebral function. Such hypotension has been
suggested as evidence for a moribund brainstem, and its presence is suggested as a criteria of cerebral death. However, vasopressor agents in all but about 20% of patients will raise the pressure above shock levels and, at times, restore the EEG.

Absence of a Remedial Lesion.—The difficulties in the clinical determination of an irreparable cerebral lesion in the emergency room may be insurmountable. The frequent combination of shock and respiratory embarrassment causes such overwhelming signs of neurological depression that a precise diagnosis is not possible before these conditions are successfully treated. Moreover, the exigencies of resuscitative measures often preclude the performance of examinations essential for an accurate early diagnosis.

Even after the vital functions have been restored, the establishment of a definitive diagnosis—if the patient’s condition has not been previously known or is not obvious—may require time-consuming examinations. If one of the common causative states (myocardial infarction, cerebral trauma, and intracranial vascular disease) is not apparent, the gamut of conditions producing coma must be explored, and, perhaps, to confirm the cause, a therapeutic test may be necessary. Certainly, the possibility of the common treatable disorders, such as drug intoxication and intracranial hematomas, should be ruled out, especially if the diagnosis is uncertain. This may require drug surveys, angiography, radioisotope scan, or computed tomography. It is possible that although the original primary condition was remediable, the brain may be dead as the result of anaoxia due to long-standing intracranial pressure. In these circumstances, a therapeutic test as well as confirmatory examinations for cerebral death are essential.

These preliminary requirements assure that the results of the application of specific criteria for cerebral death will not be misinterpreted. However, they are time-consuming; in this study, the average time (after an insult) for resuscitative measures to reestablish and stabilize the vital functions, especially the blood pressure, and for all appropriate diagnostic and therapeutic procedures to be carried out was 7.4 hours. We suggest that six hours be considered the minimal prerequisite.

**Base Criteria**

Most previous sets of criteria for cerebral death have been based on the combination of (1) cerebral unresponsiveness (deep coma), (2) apnea, and (3) EEG. No one factor alone has been considered adequate to establish a dead brain.

**Cerebral Unresponsiveness.**—In this study, the determination of cerebral unresponsiveness was sometimes (9% of cases) confused by movements of spinal reflex origin. In practice, their distinction from purposeful responses was rarely difficult.

**Apnea.**—Because of the necessity of maintaining artificial respiration, the verification of apnea was scientifically impractical, but at the bedside was readily recognized. The validity of the requirement of 15 minutes absence of spontaneous respiration was confirmed by the observation that when cerebral death was established by other criteria, removal of the respirator was rarely followed by any respiratory efforts and never by sufficient chest movement to sustain life.

**Electrocerebral Silence.**—The interpretation of the EEG in cases of suspected cerebral death is complicated by three factors: technical inadequacies, observer error (misinterpretations in the reading of the record), and the validity of a single EEG record in the diagnosis of cerebral death.¹

These difficulties may account for some reported recoveries after presumed periods of ECS. A few records reported in the literature as flat were made at gains much less than the 24V = 1 mm recommended by the Ad Hoc Committee on EEG Criteria for Cerebral Death, and some have small baseline undulations that might represent biological activity. However, these records were read by competent electroencephalographers as ECS. In this study, there was only a 3% disagreement between the review panel and the original reader, and most of the disagreement concerned the confusion of artifact for biological activity; rarely (1% of cases) did the reverse occur, i.e., that the original reader diagnosed ECS and the review panel considered that biological activity was present. Accordingly, although on critical analysis some “flat records” may be considered by reviewers who know the complete history of the case as showing biological activity, such varied opinions regarding 1% to 3% of cases are inevitable at the present stage of the art of electroencephalography.

With the increasing desire to establish an early diagnosis of cerebral death, transplant surgeons often treat the electroencephalographer to certify ECS on the basis of a single half-hour record. Provided it is possible to eliminate cases of reversible coma (such as drug intoxication), a single flat record made according to the recommendations of the American Electroencephalographic Society Ad Hoc Committee on Criteria for Cerebral Death may signify a dead brain.² In this study, if all drug-induced comas were eliminated, no patient recovered after having a 30-minute isoelectric record. This confirms the report of the American Electroencephalographic Committee on Cerebral Death that only three patients—all with drug intoxication—recovered in a series of 1,665 persons with a flat record. With smaller numbers of cases, Prior³ has concluded similarly. The validity of these findings in the early diagnosis of cerebral death is made somewhat uncertain by the fact that the time of the EEG examination relative to the cerebral insult is unknown in most of the previously cited cases. In Prior’s series, only five of her 115 cases had EEGs made within six hours of the insult. To further impugn the validity of a single record in the diagnosis of cerebral death are the isolated cases of cardiac disease,⁴ cerebral trauma,⁵ hypothermia,⁶ and encephalitis⁷ that have been reported with the return of biological activity and the regression of coma. For these reasons, many American electroencephalographers have been loath to base a diagnosis of cerebral death on a single unqualified record.⁸

If the combination of these three basic factors—cerebral unresponsiveness, apnea, and ECS—are applied to our data bank, 187 patients met these standards for cerebral death on the initial examination and 139 of these died, all presumably with dead brains. This 99% accuracy seems adequate for basic criteria. To improve this degree
of accuracy, either further EEGs or additional standards are needed. However, the EEGs of some intoxicated patients had to be taken for more than 24 hours before unequivocal signs of biological activity appeared.

Additional Criteria

Cephalic Reflexes.—Most investigators in seeking additional criteria for cerebral death have explored the cephalic or spinal reflexes. In our study, the cephalic reflexes—pupillary, corneal, oculoauditory (blink to a clap), oculocephalic (doll eyes), oculovestibular, ciliospinal, snout, cough, pharyngeal (gag), and swallowing—were noted to have varying sensitivity as indicators of brainstem dysfunction. Moreover, the addition of any one or all of these reflexes to the basic factors does not improve the accuracy of the diagnosis of brain death. Yet, semantically, the absence of brainstem function, as demonstrated by inactivity of these reflexes, should be included in the criteria of a dead brain.

State of the Pupils.—The pupils deserve special consideration. Dilated and fixed pupils, commonly thought to be present in death, occur in less than half of comatose and apneic patients. In the 187 subjects meeting all three basic factors, 128 had dilated, 44 had small, and the remainder had unequal pupils. However, the two patients with drug intoxication had small pupils. This propensity to pupillary constriction is common to most of the sedative and narcotic agents, the notable exceptions being glutethimide (Doriden) and scopolamine. The latter may usually be recognized by evidences of parasympathetic paralysis, but the former has no pathognomonic clinical manifestations, and even pupillary dilation is not a constant feature. It would seem, then, that the additional criterion of dilated fixed pupils, which would eliminate approximately 24% of the subjects meeting the original basic factors, would provide a clinical discrimination between the dormant and dead brain for all cases except the rare glutethimide intoxication that occurred only twice in this study.

Spinal Reflexes.—The spinal reflexes—tendon jerks of arms and legs—are poor indicators of the state of the brain, for of the 187 patients meeting the basic factors, 101 had absent and 71 had active reflexes; the remainder were not examined. Hence, the state of the spinal reflexes does not discriminate the dead from the dormant brains (the two patients with drug intoxication had absent spinal reflexes). Since the spinal cord is not considered as part of the brain, the omission of these reflexes as criteria poses no semantic problem.

Other Criteria for Cerebral Death.—Many European centers equate brain death with total cerebral infarction; they consider that CBF is absent in all cases of cerebral death. However, four-vessel angiography, commonly used to demonstrate CBF, is invasive, and requiring complicating radiological techniques is impractical for routine use in critically ill patients. In our study, although more than half of the patients admitted had intracranial conditions that might have been accurately diagnosed by either radiopaque or radionuclide angiography, only 17 such procedures (6% of cases) were carried out. Because of this reluctance on the part of physicians to subject these patients to an invasive technique, indirect methods of determining cerebral blood flow have been sought. Among these, bolus transit isotope curves and echocerephalography to demonstrate loss of the midline intracranial pulsations have seemed the most promising.

The validity and limitations of these tests as measures of cerebral blood flow has yet to be established, but when positive (i.e., indicative of absence of CBF), they have been associated reliably with a lethal outcome.

Other technical examinations, such as ophthalmoscopie to detect sludging in the retinal arteries; evoked potentials, particularly auditory; rheeocerephalography; and determination of the steady potentials of the brain, have been suggested as criteria of cerebral death; as yet, their value has not been established.

Minimal Criteria For Cerebral Death

The reliability of any set of examinations, each having a certain inherent error, must be critically examined, especially if they are to be applied to patients shortly after a cerebral insult. In view of these sources of possible error, the directors of this collaborative study proposed as a safeguard that a confirmatory test relating to CBF be carried out in all cases in which an early decision of cerebral death is desired, particularly if any of the criterial findings are not definitive. This would allow a diagnosis of a dead brain to be made in patients with small amounts of sedative drugs in the blood, in patients undergoing therapeutic procedures that make examination of one or more cranial nerves impossible, and in patients meeting all other criteria of cerebral death but with small, non-reacting pupils. The following set of criteria applied to this study material identified patients, all of whom died within a week with evidence of a dead brain. Accordingly, these criteria are recommended for a larger clinical trial.

Prerequisite

All appropriate diagnostic and therapeutic procedures have been performed.

Criteria (to be present for 30 minutes at least six hours after the onset of coma and apnea)

Coma with cerebral unresponsiveness
Apnea
Dilated pupils
Absent cephalic reflexes
Electrocerebral silence

Confirmatory test

Absence of cerebral blood flow

In some respects, these criteria overlap and give added assurance that errors of omission will not cause lethal mistakes. Rarely is a single clinical criterion the sole factor. However, dilated pupils alone discriminates against most cases of drug intoxication. Probably the confirmatory test need only be made if an early diagnosis of cerebral death is desired at a time when criteria have not been unequivocally met; however, the indications for this test will become apparent in a field trial. Perhaps at this time, an overlap of criteria is advisable in view of the difficulties in the determination of drug intoxications, the fallacies in clinical and laboratory tests, and the inevitable observer errors. However, the chance of even temporary survival if the proposed clinical and EEG criteria are met for 30 minutes is small, and are infinitesimal if the confirmatory test is also met.
CONCLUSION

An appraisal of the currently accepted criteria of brain death, based on data collected from a collaborative study of 503 patients with suspected cerebral death is presented.

A confirmatory test to demonstrate the absence of CBF is suggested when an early diagnosis of cerebral death is desired, particularly if one or more of the critical factors are indefinite or cannot be tested. This would allow a diagnosis of a dead brain to be made in patients with small amounts of sedative drugs in the blood, in patients who are undergoing therapeutic procedures that make examination of one or more cranial nerves impossible, and in patients with small pupils.

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Participants in this study are as follows:

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Biostatistics: Johns Hopkins University School of Hygiene, Earl Diamond, PhD*, University of New Mexico School of Medicine, Francis J. Wall, PhD (consultant).

National Institute of Neurological and Communicative Disorders and Stroke Staff: Gastono F. Molinari, MD (Project Officer); Andrew J.D. Smith, MD; John I. Moseley, MD.


References


Blaise Pascal (1623-1662), French mathematician, scientist, and philosopher, was born in 1623 at Clermont-Ferrand, Auvergne, France. Pascal, a child prodigy in mathematics, helped devise the mathematic theory of probability, which is of great importance in biomedical statistics and epidemiology. He established the guiding maxim of modern science: "that experiments are the true teachers which one must follow in physics"—in opposition to the thinking of Descartes, that human reason dictates its law to nature and is unaltered by the object it considers.

In the field of natural philosophy, Pascal carried out experiments on the equilibrium of fluids (he was one of the founders of hydrodynamics). His law states that pressure applied to a liquid at any point is transmitted equally in all directions. He also did research on barometric pressure at different altitudes. In his honor, besides Pascal's law, there is Pascal's arithmetical triangle and Pascal's mystic hexagram.

He died on Aug 19, 1662, reportedly of a carcinomatous meningitis from a malignant ulcer of the stomach, and was honored on a stamp (Scott No. 1038) issued by France in 1962 on the 300th anniversary of his death.—M. A. SHAMPO and R. A. KYLE

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