

HOW DO PHYSICIANS PROVE IRREVERSIBILITY IN THE DETERMINATION OF DEATH?*

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From the beginning of recorded time, physicians have sought reliable signs of death to prove that the vital functions of newly deceased patients had ceased. In the pre-technological era (prior to the 20th century), physicians developed numerous creative bedside tests and procedures to prove that patients were dead.¹ Nevertheless, there remained widespread public fear that physicians would incorrectly pronounce death and that patients would be buried alive as a result.² Some 18th and 19th century commentators even suggested that the signs of death physicians used were so unreliable that before pronouncing death, physicians should await the development of rigor mortis to be completely certain the patient was dead.

In our contemporary technological era, in which resuscitation and organ support is possible, the principal issue in death determination has evolved from how physicians can accurately detect the cessation of vital organ functions to how physicians can confidently determine that vital organ functions have ceased irreversibly. This question is relevant in both 'brain death' and 'circulatory death' pronouncements.³ Physicians declaring brain death must prove that the demonstrated loss of cerebral hemispheric, diencephalic, and brain stem functions is irreversible. Similarly, physi-

* The views expressed with absolute freedom in this paper should be understood as representing the views of the author and not necessarily those of the Pontifical Academy of Sciences. The views expressed in the discussion are those of the participants and not necessarily those of the Academy.

¹ Powner D.J., Ackerman B.M., Grenvik A., Medical diagnosis of death in adults: historical contributions to current controversies. *Lancet* 1996;348:1219-1223.

² Pernick M.S., Back from the grave: Recurring controversies over defining and diagnosing death in history. In: Zaner R.M. (ed): *Death: Beyond Whole-Brain Criteria*. Dordrecht: Kluwer Academic Publishers, 1988:17-74.

³ Herein I use the slogans 'brain death' and 'circulatory death' simply to denote the two separate tests for physicians to determine death. It does not intend to suggest that there is more than one type of death. There is only one type of death that may be determined two ways. 'Brain death' and 'circulatory death' both are equivalent to 'death'.

cians declaring circulatory death must prove that the loss of cardiac, respiratory, and circulatory functions is irreversible. But the proof of the irreversibility of relevant organ functions in both circumstances remains far from obvious and has subtleties requiring explanation, justification, and verification. In this article I analyze the concept of irreversibility of organ functions in brain death and circulatory death, and explain how physicians can reasonably prove that the loss of these vital functions is irreversible.

Two Tests of Death

Physicians can test for death in two ways: 1) in the patient not receiving mechanical ventilatory support, by showing the permanent or irreversible cessation of circulation and respiration; or 2) in the patient receiving mechanical ventilatory support, by showing the irreversible cessation of all clinical functions of the brain.⁴ In the United States, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research proposed a model a statute of death called the Uniform Determination of Death Act (UDDA) incorporating these two alternative determinations that subsequently was enacted in nearly all American jurisdictions. In its relevant portion, the UDDA provides:

An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards.⁵

My Dartmouth colleagues and I gently criticized the framers of the UDDA for not asserting a single brain standard of death (as the President's Commission itself had argued in *Defining Death*)⁶ that could be tested by physicians in two ways depending on the presence of ventilatory support, because it was clear that the tests showing the irreversible cessation of circulatory and respiratory functions were adequate tests of death only because they inevitably led to the irreversible cessation of all brain func-

⁴ This section is adapted in part from Bernat J.L., Are organ donors after cardiac death really dead? *Journal of Clinical Ethics* 2006;17:122-132.

⁵ President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Defining Death: Medical, Legal and Ethical Issues in the Determination of Death*. Washington, DC: U.S. Government Printing Office, 1981:72-84.

⁶ President's Commission, 1981:31-43.

tions.⁷ Because patients who were successfully resuscitated prior to the complete loss of brain functions were not dead, the loss of all brain functions was the unitary criterion of death. Thus, the bifurcated so-called 'criteria' of the UDDA are not independent, and are not truly criteria, but simply are separate tests of death to prove the unitary brain criterion.

The Meaning of 'Irreversible' Loss of Vital Functions

The concept of death requires irreversibility by its intrinsic nature because if a patient could be resuscitated successfully back to life, the patient was never dead in the first place. Thus, by definition, death is irreversible.⁸ Moreover, the requirement for irreversibility is enshrined in many statutes of death (including the UDDA) that require physicians to demonstrate that the cessation of vital functions is irreversible. But what does *irreversible* actually mean and is it the same as *permanent*? The term *irreversible* was not defined in the UDDA or other statutes.

The *Oxford English Dictionary*, second edition, defines *irreversible* as 'that cannot be undone, repealed, or annulled; irrevocable'.⁹ Thus, a loss of a function can be said to be irreversible if that function cannot possibly be regained spontaneously or restored through intervention. *Irreversible* is an absolute and univocal statement that reflects the physical reality of immutability, a condition that exists independently of our intent or action.¹⁰

The philosopher David Cole pointed out that the term *irreversible* is inherently ambiguous because it belongs to a class of modal terms in the philosophy of language that resists consensus analysis.¹¹ Cole identified two principal construals of *irreversible* functions. The strong construal of the term means that the function cannot be restored by anyone under any circumstance at any time, now or in the future. The weak construal means that the function cannot be restored by anyone now using available con-

⁷ Bernat J.L., Culver C.M., Gert B., Defining death in theory and practice. *Hastings Center Report* 1982; 12(1): 5-9.

⁸ I have defended this assertion in Bernat J.L., The biophilosophical basis of whole-brain death. *Social Philosophy & Policy* 2002;19(2): 324-342.

⁹ *Oxford English Dictionary*, 2nd ed. Oxford: Oxford University Press, 2006.

¹⁰ This section is adapted in part from Bernat J.L., Are organ donors after cardiac death really dead? *Journal of Clinical Ethics* 2006;17:122-132.

¹¹ Cole D., Statutory definitions of death and the management of terminally ill patients who may become organ donors after death. *Kennedy Institute of Ethics Journal* 1993;3:145-155; and Cole D.J., The reversibility of death. *Journal of Medical Ethics* 1992;18:26-30.

temporary technology but possibly may be able to be restored elsewhere now where emerging technologies are available or in the future with the development of new technologies. Thereafter, David Lamb pointed out that Cole's strong construal of irreversible (essentially, a return of functions that is logically impossible) fails the test of plausibility and should be rejected when applied to the definition of death.¹²

For three reasons I agree with Lamb that the weak construal of *irreversibility* of vital functions is our intended usage when applied to determining death. First, it is difficult to predict the capabilities and effects of future technologies even to assess biological possibility. Second, the availability of unanticipated future technologies may alter the concepts in question requiring a reanalysis at that time. For example, we may need to redefine human death if future technologies permit brain synthesis or brain transplantation. But, most importantly, the issue of death determination, governed by a statute of death, concerns the current possibility of the reversal of ceased vital functions. And I agree with John Lizza when he pointed out that our use of irreversibility in a definition of death implicitly refers to practical and not logical factors about the physical state of the person.¹³

The Meaning of 'Permanent' Loss of Vital Functions

Some scholars have used the term *permanent* synonymously with *irreversible* but there is an important distinction between the two terms when describing loss of vital functions in determining death.¹⁴ Although on first impression, *permanent* and *irreversible* seem synonymous, they have an important distinction. The *Oxford English Dictionary*, second edition defines *permanent* as 'continuing or designed to continue indefinitely without change; abiding, lasting, enduring, persistent (opposed to *temporary*)'. Thus, a loss of function can be said to be permanent if that function will not become restored either spontaneously or through intervention. *Permanent* is an equivocal and contingent condition that permits possibili-

¹² Lamb D., Reversibility and death: a reply to David J. Cole. *Journal of Medical Ethics* 1992;18:31-33.

¹³ Lizza J., Potentiality, irreversibility, and death. *Journal of Medicine and Philosophy* 2005;30:45-64.

¹⁴ This section is adapted in part from Bernat J.L., Are organ donors after cardiac death really dead? *Journal of Clinical Ethics* 2006;17:122-132.

ty. It may rely on our intent and action to be realized, and does not refer directly to a possibility of reversal.

Despite their distinct definitions, a spatial and temporal relationship exists between the sets of permanently and irreversibly lost functions. The set of permanently lost functions encompasses the set of irreversibly lost functions. Thus, all functions that are irreversibly lost also are permanently lost but not all functions that are permanently lost are necessarily irreversibly lost, at least at the moment that permanence is first established. And all functions that are irreversibly lost are first permanently lost, that is, once a function becomes permanently lost it quickly evolves to also being irreversibly lost. The important issue I discuss here is whether physicians declaring death can confidently rely on the permanent cessation of vital organ function or whether they must seek proof of irreversible cessation of function.

An Analysis of 'Brain Death'

Brain death is the common and colloquial (but misleading) term that refers to the determination of human death by showing the irreversible cessation of all clinical brain functions.¹⁵ Determining human death by a brain criterion is based on the concept that death is best defined as the cessation of functioning of the organism as a whole and that irreversible cessation of clinical brain functions is the criterion fulfilling the definition because the brain provides the critical functions of the organism as a whole and therefore its destruction is both a necessary and sufficient condition for death.¹⁶ My Dartmouth colleagues and I have offered a rigorous analysis of why brain death and human death are equivalent based on these concepts.¹⁷ Our analysis was accepted by the U.S. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in their influential book *Defining Death*,¹⁸ and is regarded by many scholars as the standard paradigm of

¹⁵ This section is adapted, in part, from Bernat J.L., The whole-brain concept of death remains optimum public policy. *Journal of Law, Medicine & Ethics* 2006;34:35-43.

¹⁶ Bernat J.L., The biophilosophical basis of whole-brain death. *Social Philosophy & Policy* 2002;19(2):324-342.

¹⁷ Bernat J.L., Culver C.M., Gert B., On the definition and criterion of death. *Annals of Internal Medicine* 1981;94:389-394.

¹⁸ President's Commission, 1981:35-36.

brain death.¹⁹ In response to critics, I have refined this account several times over the past quarter-century.²⁰

Brain death as a determination of human death currently is accepted by physicians, medical organizations, legislators, and societies through the Western developed world and much of the non-Western undeveloped world.²¹ Indeed, brain death generally is regarded as a formerly controversial bioethical and biophilosophical issue for which the greatest consensus has developed, permitting the development of more or less uniform standards for determining death around the world.²² Importantly, despite the continued publication of scholarly articles arguing that brain death is not the equivalent of human death and that it is illogical, unnecessary, or an anachronism, these authors have failed to convince medical societies or lawmakers in any country to abandon brain death determinations. In fact, the opposite is the case. Over the past generation, more countries than ever before are practicing brain death.²³

Brain death advocates can be divided into one major and two minor camps based on the amount of brain destruction that constitutes the criterion of death. These camps are often informally known as the 'whole-brain', 'brain stem', and 'higher brain' formulations.²⁴ Those who advocate the

¹⁹ This claim was made recently, for example, by Shewmon D.A., Shewmon E.S., The semiotics of death and its medical implications. *Advances in Experimental Medicine and Biology*, 2004;550:89-114; and Chiong W., Brain death without definitions. *Hastings Center Report* 2005;35(6):20-30.

²⁰ See Bernat J.L., The definition, criterion, and statute of death. *Seminars in Neurology* 1984;4:45-52; Bernat J.L., How much of the brain must die in brain death? *Journal of Clinical Ethics* 1992;3:21-26; Bernat J.L., A defense of the whole-brain concept of death. *Hastings Center Report* 1998;28(2):14-23; Bernat J.L., The biophilosophical basis of whole-brain death. *Social Philosophy & Policy* 2002;19(2): 324-342; and Bernat J.L., The concept and practice of brain death. *Progress in Brain Research* 2005;150:369-379.

²¹ Wijdicks E.F.M., Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology* 2002;58:20-25.

²² Capron A.M., Brain death – well settled yet still unresolved. *New England Journal of Medicine* 2001;344: 1244-1246.

²³ I have summarized many of the arguments against brain death in: Bernat J.L., A defense of the whole-brain concept of death. *Hastings Center Report* 1998;28(2):14-23; Bernat J.L. The biophilosophical basis of whole-brain death. *Social Philosophy & Policy* 2002;19(2):324-342; and Bernat J.L., The concept and practice of brain death. *Progress in Brain Research* 2005;150:369-379. For data on the international acceptance of brain death, see Wijdicks E.F.M., Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology* 2002;58:20-25.

²⁴ Bernat J.L., How much of the brain must die in brain death? *Journal of Clinical Ethics* 1992;3:21-26.

whole-brain criterion of death comprise the large majority and represent nearly all laws and practices outside of the UK and a few other countries where the brain stem formulation is used. The higher-brain formulation has been advocated by a small group of philosophers and a few others but has never achieved acceptance in any jurisdiction and is accepted and practiced nowhere in the world.

The whole-brain criterion requires cessation of all brain clinical functions including those of the cerebral hemispheres, diencephalon (thalamus and hypothalamus), and brain stem. Whole-brain advocates require global cessation of neuronal functions because each part of the brain serves some of the critical functions of the organism as a whole. The brain stem initiates and controls breathing, regulates circulation, and serves as the generator of wakefulness through the reticular system that is a physiological prerequisite for conscious awareness. The diencephalon provides the center for bodily homeostasis, regulating and coordinating numerous neuroendocrine control systems such as those regulating body temperature, salt and water regulation, feeding behavior, and memory. The cerebral hemispheres have an indispensable role in awareness that provides the conditions for all conscious behavior that serves the health and survival of the organism.

Clinical functions are those that are measurable at the bedside. The distinction between the brain's clinical functions and brain activities, recordable electrically, chemically, or through other laboratory means, was made by the President's Commission in *Defining Death*.²⁵ All clinical brain functions measurable at the bedside must be lost and their cessation must be shown to be irreversible. But the whole-brain criterion does not require the loss of all neuronal activities. Some neurons may survive individually or in small clusters that may contribute to recordable brain activities (by an electroencephalogram, for example) but not to clinical functions.²⁶ The precise minimum number, location, and configuration of neurons necessary and sufficient for death remains unknown.

Despite the fact that the whole-brain criterion does not require the cessation of functioning of every brain neuron, it does rely on a pathophysiological process known as brain herniation to assure widespread destruction

²⁵ President's Commission, 1981:28-29.

²⁶ See description of residual E.E.G. activity in some brain dead patients in Grigg M.M., Kelly M.A., Celesia C.G., Ghobrial M.W., Ross E.R., Electroencephalographic activity after brain death. *Archives of Neurology* 1987;44:948-954.

of the neuron systems responsible for the brain's clinical functions.²⁷ When the brain is injured diffusely by trauma, hypoxic-ischemic damage during cardiorespiratory arrest or asphyxia, meningoencephalitis, or enlarging intracranial mass lesions such as neoplasms,²⁸ resulting brain edema causes intracranial pressure to rise to levels exceeding mean arterial blood pressure. At this point, intracranial circulation ceases and nearly all brain neurons that were not destroyed by the initial brain injury are secondarily destroyed by the cessation of intracranial circulation. Thus the whole-brain formulation provides a fail-safe mechanism to eliminate false-positive brain death determinations and assure the loss of the critical functions of the organism as a whole. Showing the absence of all intracranial circulation is sufficient to prove widespread destruction of all critical neuronal systems.

An Analysis of 'Circulatory Death'

Circulatory death is the basis for determining death by showing the irreversible absence of heartbeat, circulation, and breathing. It is a common means for physicians to determine death in patients for whom mechanical ventilatory support is neither provided nor planned. It produces the criterion of death once the brain has become completely destroyed by hypoxic-ischemic infarction. It is the means of death determination in essentially all non-hospitalized patients and in about 99% of hospitalized patients. Until recently, there was no controversy in determining circulatory death. However, the introduction of hospital programs of organ donation after cardiac death (formerly called 'non-heart-beating organ donation') have highlighted the issue of how long circulation must cease before death can be declared, and created a controversy that has been only partially resolved.²⁹

Organ donation after cardiac death (DCD) has become a widespread practice in the United States over the past decade. In the early 1990s, in response to the growing demand for organs to transplant and to the desires

²⁷ Plum F, Posner J.B., *The Diagnosis of Stupor and Coma*, 3rd ed. Philadelphia: FA Davis Co, 1980:88-101.

²⁸ These are the most common causes of brain death. See Staworn D., Lewison L., Marks J., Turner G., Levin D., Brain death in pediatric intensive care unit patients: incidence, primary diagnosis, and the clinical occurrence of Turner's triad. *Critical Care Medicine* 1994;22:1301-1305.

²⁹ This section is adapted in part from Bernat J.L., Are organ donors after cardiac death really dead? *Journal of Clinical Ethics* 2006;17:122-132.

of the families of brain-damaged but non-brain-dead patients being removed from life-sustaining therapy in ICUs to have their loved ones serve as organ donors, the University of Pittsburgh Medical Center established the first modern DCD program.³⁰ Since then, greater numbers of American organ procurement organizations (OPOs) have encouraged DCD programs so that approximately half the OPOs in the United States now permit DCD.³¹ The growth and acceptance of DCD programs was spurred by two influential reports from the Institute of Medicine in 1997 and 2000 that concluded that DCD was legitimate and desirable, and hospitals should be encouraged to implement DCD protocols.³²

DCD protocols permit a hopelessly dying, ventilator-dependent patient (or, more commonly, her legally-authorized surrogate) to consent for organ donation after death once further life-sustaining therapy has been refused and discontinued. In the most common case, the patient has sustained profound brain damage from trauma, stroke, or cardiac arrest that creates ventilator-dependency and offers no hope for meaningful neurological recovery. Such a patient does not meet brain death criteria but is hopelessly ill because of profound brain damage with a very poor prognosis. Based upon the patient's prior wishes for stopping treatment in light of the poor prognosis, the family then refuses further life-sustaining therapy on behalf of the patient to permit her to die. They also request or consent to her organ donation after death.

DCD protocols coordinate the planning and timing of withdrawing the ventilator with the organ procurement team's readiness to procure organs. Once withdrawn from the ventilator, patients usually cannot breathe at all or breathe insufficiently to maintain life.³³ As the patient's

³⁰ University of Pittsburgh Medical Center Policy and Procedure Manual. Management of terminally ill patients who may become organ donors after death. *Kennedy Institute of Ethics Journal* 1993;3:A1-A15.

³¹ The most current American DCD data were reported in Bernat J.L., D'Alessandro A.M., Port F.K., et al., Report of a national conference on donation after cardiac death. *American Journal of Transplantation* 2006;6:281-291.

³² Institute of Medicine. *Non-Heart-Beating Organ Transplantation: Medical and Ethical Issues in Procurement*. Washington DC: National Academy Press, 1997; and Institute of Medicine. *Non-Heart-Beating Organ Transplantation: Practice and Protocols*. Washington DC: National Academy Press, 2000.

³³ Approximately 25% of patients in DCD protocols, following ventilator removal, continue to breathe and have heartbeat for greater than one hour before they die, rendering them unsuitable for DCD for logistical reasons. See Delmonico F.L., Sheehy E., Marks W.H., Baliga P., McGowan J.J., and Magee J.C., Organ donation and utilization in the United States, 2004. *American Journal of Transplantation* 2005;5(Part 2):862-873.

oxygenation rapidly declines, her heartbeat then stops from lack of oxygen. After five minutes of absent heartbeat, the patient is declared dead and rushed to the operating room where organ procurement is rapidly performed, usually yielding transplantable kidneys, liver, and occasionally other organs.

An important unresolved controversy over the conceptual foundation of DCD is whether the organ donors are truly dead at the moment they are declared dead according to most DCD protocols, namely after five minutes³⁴ of asystole³⁵. Several scholars have argued that a DCD patient may not be dead after five minutes of asystole³⁶ because if the patient's heart could be restarted at a point before the brain was totally destroyed by ischemic infarction from lack of circulation, the patient would not be dead. I have argued recently that the answer to this important question turns on the distinction between the *permanent* and *irreversible* loss of circulatory and respiratory functions as a test of death. I concluded that the organ donors are dead at the point that their circulation permanently ceased.³⁷

³⁴ American organ procurement organization DCD protocols vary on the stipulated length of time of asystole required to declare death. Most have adopted the Institute of Medicine's recommendation of five minutes but two use two minutes. In the Netherlands they wait ten minutes.

³⁵ DCD protocols usually use the term 'asystole' not meaning an absence of recordable electrocardiographic activity, but meaning an absence of mechanical cardiac activity sufficient to generate a pulse or blood flow. When the heart stops after apnea, the cardiac rhythm usually diminishes gradually before stopping, but the resultant weak cardiac electrical signal is insufficient to produce a cardiac contraction necessary to create a pulse or blood flow. This condition of absent pumping despite a present cardiac rhythm, known as pulseless electrical activity, precedes the total absence of cardiac electrical activity. But it is simpler merely to say 'asystole' because heartbeat and circulation stops even if an ineffectual cardiac signal persists temporarily. This phenomenon has been studied in a series of patients. See Wijdicks E.F.M. and Diringner M.N., Electrocardiographic activity after terminal cardiac arrest in neurocatastrophes. *Neurology* 2004;62:673-674.

³⁶ See, for example, Lynn J., Are the patients who become organ donors under the Pittsburgh protocol for 'non-heart-beating donors' really dead? *Kennedy Institute of Ethics Journal* 1993;3:167-78; Truog R.D., Is it time to abandon brain death? *Hastings Center Report* 1997;27(1):29-37; and Youngner S.J., Arnold R.M., DeVita M.A., When is 'dead'? *Hastings Center Report* 1999;29(6):14-21.

³⁷ Bernat J.L., Are organ donors after cardiac death really dead? *Journal of Clinical Ethics* 2006;17:122-132.

Proving Irreversibility in Brain Death

Every set of brain death tests requires that the measured loss of clinical functions be the result of an irreversible pathological process.³⁸ Thus, pre-conditions for all brain death tests require the absence of depressant drug intoxications, severe hypothermia, and neuromuscular blockade, each of which could mimic the signs of brain death but be potentially reversible by intensive medical treatment. Most set of brain death tests (notably those recommended by the U.S. President's Commission and the American Academy of Neurology³⁹) require a demonstrable structural brain lesion that is sufficient to produce the clinical signs, to minimize the chances of a metabolic or toxic cause that might be reversible. Clinical irreversibility is demonstrated by: 1) demonstrating a structural lesion adequate to cause the signs of loss of brain functions; 2) excluding reversible causes; and 3) conducting serial examinations separated by an interval of hours to show no recovery. Although this plausible clinical claim for irreversibility is usually accepted, it is not self-evidently true and its empirical basis is limited to a few studies.⁴⁰

We know that some examiners declaring brain death are careless in performing, interpreting, or recording the clinical tests, particularly the apnea test.⁴¹ Despite the presence of standardized, widely accepted, and highly publicized guidelines for brain death determination,⁴² physicians perform

³⁸ This section is adapted in part from: Bernat J.L., On irreversibility as a prerequisite for brain death determination. *Advances in Experimental Medicine and Biology* 2004;550: 161-167.

³⁹ President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Defining Death: Medical, Legal and Ethical Issues in the Determination of Death*. Washington, DC: U.S. Government Printing Office, 1981:Appendix F; and The Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters for determining brain death in adults [summary statement]. *Neurology* 1995;45:1012-1014.

⁴⁰ For example, see NIH Collaborative Study of Cerebral Survival. An appraisal of the criteria of cerebral death. *JAMA* 1977;237:982-986.

⁴¹ See Earnest M.P., Beresford H.R., McIntyre H.B., Testing for apnea in brain death: methods used by 129 clinicians. *Neurology* 1986;36:542-544; and Mejia R.E., Pollack M.M., Variability in brain death determination practices in children. *JAMA* 1995;274:550-553.

⁴² See Wijdicks E.F.M., Determining brain death in adults. *Neurology* 1995;45:1003-1011, The Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters for determining brain death in adults [summary statement]. *Neurology* 1995;45:1012-1014; and Wijdicks E.F.M., The diagnosis of brain death. *New England Journal of Medicine* 2001;344:1215-1221.

it incorrectly in many settings. It is not solely unskilled examiners at fault. A recent study from a prestigious medical center demonstrated the inadequacies of the methods and recordings of routine brain death determinations.⁴³ Therefore, I believe it is probable that some of the reported cases of 'chronic brain death' by Alan Shewmon, in which the heartbeat and systemic circulation of diagnosed brain dead patients had been technologically maintained for many months or longer, represented cases of profound brain damage who had been improperly declared brain dead.⁴⁴

The surest method to demonstrate that the global loss of clinical brain functions is irreversible is to show the complete absence of intracranial blood flow. Brain neurons are damaged after just a few minutes of lack of blood flow and are globally destroyed when blood flow completely ceases for more than 20-30 minutes.⁴⁵ Thus, showing a total absence of intracranial blood flow that has persisted for more than 30 minutes proves the irreversibility as well as the totality of the loss of clinical brain functions. Blood flow to the brain is tightly regulated by the homeostatic system of cerebral autoregulation that operates over a wide range of systemic blood pressures to assure adequate cerebral perfusion pressures. Normal cerebral autoregulatory mechanisms can be disturbed when systemic blood pressures become excessively high or low, or when intracranial pressure rises to very high levels.

Traumatic and vascular global brain lesions leading to brain death produce diffuse cerebral edema. The cerebral edema results in an increase in intracranial contents but intracranial volume remains fixed by the rigid skull. Consequently, intracranial pressure (ICP) rises. In most brain death cases, intracranial pressure rises until it exceeds mean arterial blood pressure. In many instances of massive head trauma and massive subarachnoid hemorrhage, ICP exceeds systolic blood pressure. When ICP exceeds systolic blood pressure, no blood can enter the cranial vault and the brain loses all circulation. When ICP is lower than systolic blood pressure but higher than diastolic pressure but exceeds mean arterial pressure, blood enters the cranium and brain during systole but is pushed back an equal amount during diastole. This phenomenon of so-called 'reverberating' or 'oscillating'

⁴³ Wang M.Y., Wallace P., Gruen J.B., Brain death documentation: analysis and issues. *Neurosurgery* 2002;51:731-735.

⁴⁴ Shewmon D.A., Chronic 'brain death': meta-analysis and conceptual consequences. *Neurology* 1998;51:1538-1545.

⁴⁵ Miyamoto O., Auer R.N., Hypoxia, hyperoxia, ischemia, and brain necrosis. *Neurology* 2000;54:362-371.

flow cannot result in perfusion of the brain because it produces no net forward circulation. Thus, whether there is no intracranial systolic blood flow or there is no net blood flow because of reverberating flow, the brain becomes diffusely and irreversibly destroyed within minutes.

The clinical examination evidence of absent intracranial blood flow is the presence of one of the syndromes of cerebral transtentorial herniation, as shown by Fred Plum and Jerome Posner (1980).⁴⁶ Central and uncal transtentorial herniation of the midbrain, results from intracranial tissue shifts caused by the development of lateralized intracranial pressure cones from an expanding mass lesion. The lateralized pressure cones induce a caudal shift of brain tissue that secondarily destroys brain stem neurons through a progressive pressure gradient-induced ischemia. All neurology residents are taught to seek the clinical evidence of these herniation syndromes because once the brain stem has been infarcted during transtentorial herniation, the loss of brain clinical functions has become irreversible.

An important added significance of requiring herniation syndromes resulting from raised ICP is that it provides proof that the destruction of brain neurons is widespread. The whole-brain criterion of death requires that all clinical functions of the brain cease irreversibly. Once full herniation has been completed and all intracranial blood flow has stopped, examiners declaring brain death can be confident that neuronal damage is widespread and that the herniation has eliminated all clinical functions of the brain. Thus, requiring a demonstration of absence of intracranial blood flow at once confirms both irreversibility and totality of the cessation of neuronal function. But it is essential that a total absence of intracranial blood flow not be confused with only a reduction of intracranial blood flow. In studies of the ischemic penumbra surrounding lesions in purportedly brain dead patients, Cicero Coimbra showed the importance of distinguishing between these two situations and emphasized the serious errors that can occur if they are confused.⁴⁷

Tests showing absent intracranial circulation have confirmed brain death for over three decades.⁴⁸ Contrast arteriography was first used in

⁴⁶ Plum F., Posner J.B., *The Diagnosis of Stupor and Coma*, 3rd ed. Philadelphia: FA Davis Co, 1980:88-101.

⁴⁷ Coimbra C.G., Implications of ischemic penumbra for the diagnosis of brain death. *Brazilian Journal of Medical and Biological Research* 1999;32:1479-1487.

⁴⁸ These tests have been reviewed in: Young B., Lee D., A critique of ancillary tests of brain death. *Neurocritical Care* 2004;1:499-508.

the 1970s to show absence of intracranial circulation distal to the intracranial portions of the internal carotid and vertebral arteries. It continues to be used by physicians in some settings that lack access to simpler alternative techniques. Its principal drawbacks are its invasiveness, the fact that high injection pressures can force transient intracranial blood flow that would not occur otherwise, and that the patient must be transported to the radiology suite.⁴⁹

Intravenous radionuclide angiography was first used in the 1980 to prove absent intracranial circulation. An intravenous infusion of the radioisotope pertechnetate is infused intravenously. The patient undergoes static and dynamic radionuclide brain scanning to measure entry of the radioisotope into the brain. Dynamic images show the isotope stopping as the internal carotid and vertebral arteries enter the dura mater. Static images show only the presence of isotope in the scalp and face because of the patency of the external carotid artery and its branches.⁵⁰ A radiologist or nuclear medicine expert who is experienced in this technique can confidently interpret absence of blood flow in the brain. Shortcomings of intravenous radionuclide angiography are the difficulty in distinguishing slight vs. absent blood flow in the posterior circulation and that the patient must be transported to the nuclear medicine suite.

Transcranial Doppler (TCD) ultrasound was perfected in the 1990s and now is the test used in many medical centers to document cessation of intracranial circulation in brain death.⁵¹ TCD ultrasound can be performed in the patient's bed in the ICU. Current standards require three separate insonation sites.⁵² Reproducible images of intracranial pulses usually can be obtained if they are present. Two principal patterns of TCD ultrasound abnormalities have been documented in brain death: absent systolic spikes

⁴⁹ Bradac G.B., Simon R.S., Angiography in brain death. *Neuroradiology* 1974;7:25-28.

⁵⁰ Goodman J.M., Heck L.L., Moore B., Confirmation of brain death with portable isotope angiography: a review of 204 consecutive cases. *Neurosurgery* 1985;16:492-497; and Newberg A., Alavi A., van Rhijn S., Cotter A., Reilly P., Radiologic diagnosis of brain death. *JAMA* 2002;288:2121-2122.

⁵¹ Petty G.W., Mohr J.P., Pedley T.A., *et al.*, The role of transcranial Doppler in confirming brain death: sensitivity, specificity, and suggestions for performance and interpretation. *Neurology* 1990;40:300-303.

⁵² Ducrocq X., Braun M., Debouverie M., Junges C., Hummer M., Vespignani H., Brain death and transcranial Doppler: experience in 130 cases of brain dead patients. *Journal of Neurological Sciences* 1998;160:41-46.

and reverberating flow. Systolic spikes are absent when ICP exceeds systolic blood pressure because no measurable systolic flow can be conducted to the intracranial arteries. When ICP exceeds mean arterial blood pressure but is lower than systolic blood pressure, reverberating flow is seen. Blood advances during systole but is pushed back an equal amount during diastole because intracranial pressure exceeds diastolic blood pressure. Both patterns confirm the complete absence of intracranial circulation.⁵³ The principal limitation to TCD ultrasound is that the results are operator-dependent.

More recently, emerging imaging techniques have been applied to this problem. There are several studies using single photon emission computed tomography (SPECT) scintigraphy with the radioisotope Tc-99m HMPAO that validate the complete absence of intracranial blood flow in brain death by this relatively simple technique.⁵⁴ Several case reports have been published demonstrating absent intracranial blood flow by magnetic resonance angiography (MRA), magnetic resonance (MRI) diffusion-weighted and perfusion-weighted imaging, and computed tomography angiography (CTA).⁵⁵ These newer techniques may replace the older ones once they have been more completely validated.

In a recent article, I suggested that a confirmatory test showing cessation of intracranial blood flow should become customary for a brain death declaration, at least if there is any difficulty in performing or interpreting the clinical testing.⁵⁶ However, the tests showing absent intracranial blood flow are useful only acutely when intracranial pressure is at its highest. If cardiopulmonary support of the brain dead patient is continued, cerebral edema subsides thereafter and ICP begins to fall within hours to days. Once ICP has fallen to a level lower than mean arterial pressure, intracranial cir-

⁵³ Ducrocq X., Hassler W., Moritake K., *et al.*, Consensus opinion on diagnosis of circulatory arrest using Doppler-sonography. *Journal of Neurological Sciences* 1998;159:145-150.

⁵⁴ Wilson K., Gordon L., Selby J.B. Jr., The diagnosis of brain death with Tc-99m HMPAO. *Clinics in Nuclear Medicine* 1993;18:428-434; Donohoe K.J., Frey K.A., Gerbaudo V.H., Mariani G., Nagel J.S., Shulkin B., Procedural guidelines for brain death scintigraphy. *Journal of Nuclear Medicine* 2003;44:846-851; and Munari M., Zucchetta P., Carollo C., *et al.*, Confirmatory tests in the diagnosis of brain death: comparison between SPECT and contrast angiography. *Critical Care Medicine* 2005;33:2068-2073.

⁵⁵ Lovblad K.O., Bassetti C., Diffusion-weighted magnetic resonance imaging in brain death. *Stroke* 2000;31:539-42; Qureshi A.I., Kirmani J.F., Xavier A.R., Siddiqui A.M., Computed tomographic angiography for diagnosis of brain death. *Neurology* 2004;62:652-653.

⁵⁶ Bernat J.L., On irreversibility as a prerequisite for brain death determination. *Advances in Experimental Medicine and Biology* 2004;550:161-167.

circulation restarts ('reflow') at least to a limited degree in the necrotic brain.⁵⁷ The so-called 'respirator brain', described by Earl Walker and colleagues in the 1970s, is a result of neuronal and glial liquifactive necrosis in the setting of intracranial reflow once ICP has dropped.⁵⁸ Once ICP has fallen, physicians should instead use tests to confirm absent brain electrical signals (the battery of electroencephalography, brain stem auditory evoked responses, and somatosensory evoked responses) because blood flow testing may show a false negative confirmation of brain death because of renewed blood flow to the necrotic brain.⁵⁹

Proving Irreversibility in Circulatory Death

In most circulatory death determinations in the hospital, merely detecting the loss of breathing, heartbeat, and circulation is sufficient to declare death. Physicians can determine that the loss of these functions is permanent because they know that once breathing and heartbeat cease for several minutes, they will not automatically restart ('auto-resuscitation'), and that no artificial resuscitation is planned. In the large majority of hospital circulatory death determinations, a long time elapses during the interval between the time the loss of vital functions is detected and the time a physician is summoned to declare death and completes an examination. This elapsed time usually is sufficient to allow a permanent loss of vital functions to progress to becoming irreversibly lost by the time death is declared.

For example, consider a dying patient with widely metastatic cancer who is admitted to the hospital for palliative care and who is expected to die in hours to days. The patient has a Do-Not-Resuscitate order and is receiving intravenous morphine. When the patient later is noted on nursing rounds to be without pulse or breathing and a house physician is called to declare death, the physician pronounces death once she demonstrates the absence of breathing and heartbeat. The physician does not need to prove

⁵⁷ Schroder R., Later changes in brain death: signs of partial recirculation. *Acta Neuropathologica* (Berlin) 1983;62:15-23.

⁵⁸ Walker A.E., Diamond E.L., Moseley J., The neuropathological findings in irreversible coma: a critique of the 'respirator brain'. *Journal of Neuropathology and Experimental Neurology* 1975;34:295-323.

⁵⁹ EEG and evoked potential tests to confirm brain death have been reviewed in: Wijdicks E.F.M., The diagnosis of brain death. *New England Journal of Medicine* 2001;344:1215-1221; and Young B., Lee D., A critique of ancillary tests of brain death. *Neurocritical Care* 2004;1:499-508.

that the loss of these vital functions is irreversible to declare death. That they are permanently lost is sufficient grounds for death determination. Thus, despite the fact that statutes of death generally include the requirement of an irreversible cessation of vital functions, the prevailing medical standard for employing the circulatory criterion of death always has been to determine that the cessation of these functions is permanent. Permanence always has been sufficient clinical grounds for determining irreversibility.

In a recent paper, I argued that vital function permanence should be sufficient to establish their irreversibility because circulatory death determinations in DCD should require a medical practice standard that is no higher than that employed when it is used in other hospitalized patients.⁶⁰ But this social question is a matter for medical societies, hospital policies, and public laws to decide.

The Time of Death

In an article analyzing the precise timing of death, Joanne Lynn and the late Ronald Cranford asserted four possible choices for stating the time of death based on the loss of functions critical to life: 'T1' when the critical function is lost; 'T2' when the critical function is observed to be lost; 'T3' when the critical function is irreversibly lost; and 'T4' when the critical function is demonstrated to be irreversibly lost.⁶¹ I have argued elsewhere that T4 is the most defensible time because death determination customarily is made in retrospect.⁶² This practice is applicable to both brain death and circulatory death determinations.

Future Directions

The doctrines of brain death and circulatory death are well-established and function successfully throughout the world without significant problems. One future goal in brain death determination is to refine with greater

⁶⁰ Bernat J.L., Are organ donors after cardiac death really dead? *Journal of Clinical Ethics* 2006;17:122-132.

⁶¹ Lynn J., Cranford R.E., The persisting perplexities in the determination of death. in Youngner S.J., Arnold R.M., Schapiro R. (eds), *The Definition of Death: Contemporary Controversies*. Baltimore: Johns Hopkins University Press, 1999:101-114.

⁶² Bernat J.L., The biophilosophical basis of whole-brain death. *Social Philosophy & Policy* 2002;19(2):324-342.

precision the exact physiological criterion of death: that precise array of neurons whose irreversible functional loss is both necessary and sufficient for death. This array probably will be a critical subset of the neurons generating the clinical functions of the cerebral hemispheres, diencephalon, and brain stem. A second goal is to work toward an international consensus on the clinical tests for brain death to achieve uniformity of testing throughout the world. A third goal is the gain consensus on the role of confirmatory testing in brain death, which I believe should be used more routinely than is presently practiced in many countries. Finally, it would desirable to resolve the conceptual debate over the coherence of the brain death doctrine but this goal seems improbable.

For circulatory death, an important future goal is to achieve consensus that demonstrating the permanent loss of respiratory and circulatory functions is sufficient to determine that their loss also is irreversible. More medical centers need to systematically record data on the occurrence and timing of 'auto-resuscitation' in patients who suffer cardiac arrest after they are removed from ventilatory support at their wish. These data will answer the empirical question of the minimum time of asystole required to prove that circulatory function has permanently ceased.

These advances will contribute to a better scientific understanding of the moment of death and an enhanced precision of its determination. They also will reassure the public that physicians can confidently and correctly determine death and that multi-organ procurement will occur only after the patient has been declared dead.