Consciousness, Coma, and Brain Death—2009

SUMMARY OF THE ORIGINAL ARTICLE

A Definition of Irreversible Coma: Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death

Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death

JAMA. 1968;205(6):337-340.

This landmark classic article was the first to quantitatively define the clinical and laboratory criteria used to measure the presence of brain death. The study included "only those comatose individuals who have no discernible central nervous system activity." Criteria to establish the presence of irreversible coma included (1) unreceptivity and unresponsitivity; (2) no movements or breathing; (3) no reflexes (brain stem); and (4) flat electroencephalogram. These criteria are still considered to be reliable and acceptable by the medical community and have become established into law, which states that brain death is equivalent to death and that all artificial support systems sustaining heart, respiratory, and metabolic functions can be legally stopped.

See www.jama.com for full text of the original *JAMA* article.

Commentary by Roger N. Rosenberg, MD

Coma refers to the clinical state in which a patient is unarousable and does not respond to stimuli. It may be caused by structural lesions to the brainstem, the thalamus, or the cerebral hemispheres, and by metabolic abnormalities.

Coma must be differentiated from the stuporous state in which the patient is unresponsive but with stimuli shows some evoked activity.[1] It must be distinguished from the persistent vegetative state (PVS),[2] a syndrome with several causes in which the patient has sustained severe brain damage, and in which coma has advanced to a state of wakefulness without detectable awareness. In addition, the minimal conscious state[3] has been described in which the patient exhibits definite responsiveness that is cognitively driven, rather than unconscious reflexive responses. There may be a progressive improving continuum from coma to PVS and then to minimal conscious state. The continuum can also proceed in an adverse manner with deterioration from coma to brain death, an irreversible clinical condition in which, by neurological examination, the patient has lost all brain stem reflexes, including any respiratory response to hypercapnea exceeding an arterial $Paco_2$ of 60 mm Hg; and has normal routine clinical chemistry results, negative toxicology screen, normal body temperature, and absence of brain blood flow by diagnostic imaging procedures.[4]

Today neurologists routinely assess patients with impaired consciousness by performing a complete neurological examination to determine if the patient is stuporous, comatose, in PVS, or in a minimal conscious state. The challenge is then to determine if the basis for the altered level of consciousness is due to a structural lesion such as an infarction, hemorrhage, tumor, infection in the brain stem, thalamus, or cerebral hemispheres; or alternatively, due to a metabolic cause such as severe hypoglycemia, electrolyte disturbance, toxin or drug overdose. The neurological examination is crucial for determining the neuroanatomical level of the cause for evaluating whether there are specific brain stem signs such as cranial nerve defects, altered patterns of respiration, the presence of hemiplegia in relation to any cranial nerve deficits, and the occurrence of focal seizures such as myoclonus or focal motor seizures. Additional causes, including herniation syndromes (transtentorial, uncal, and cerebellar), are identifiable through a careful and thorough neurological examination.[1]

See also Patient Page.

Author Affiliations: Department of Neurology and Alzheimer's Disease Center, University of Texas Southwestern Medical Center, Dallas.
Corresponding Author: Roger N. Rosenberg, MD, Department of Neurology and Alzheimer's Disease Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390 (roger.rosenberg@utsouthwestern.edu).

Coma as a clinical state has ancient roots, but the identification and precise codification of specific clinical neurological criteria for brain death causal of irreversible coma was first published in a now classic article in *JAMA* in 1968.[5] The criteria for brain death enumerated in this article have surely held up during the past 40 years. As reviewed by Joynt in 1984,[6] the Harvard criteria, as defined in the classic article for brain death, subsequently has had far-reaching positive consequences. The review[6] pointed out the potential clinical circumstance, a disparity that has been well documented, that a patient may have a dead brain in an otherwise healthy body and second, identification of an irreversible state of coma has made possible the ethical and practical donation of living organs from patients with brain death. The Uniform Determination of Death Act (http://www.hhs.gov/ohrp/documents/19830728.pdf) presented to President Reagan in 1981 stated: "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." The denotation of a patient with brain death has become equated legally to the actual death of the patient by US state legislatures and has been upheld by the courts. Publication of these articles in *JAMA* has had a significant and positive effect on the practice of neurology and on the proper medical and ethical means of deciding the prognosis of the comatose patient in general, and the patient with brain death in particular.

During the past 20 years, PVS and the minimal conscious state have been defined as being separate and identifiable from the comatose state. Positive developments include reports of patients in PVS regaining consciousness within a few weeks. Consciousness may be regained after being in PVS within the first 6 months, although regaining consciousness after 1 year in PVS is infrequent. Additional issues involve recovery of consciousness and recovery of function. The former refers to regaining wakefulness, awareness, and self-awareness. The latter includes meaningful interaction and comprehensiveness with others and the environment, the ability to learn, care for self, and participation in life's activities. Clearly, a meaningful and functional return to consciousness occurs with regularity from PVS and also from the minimal conscious state. It is, therefore, vital for the clinician to observe and recognize a patient's emergence from PVS into the minimal conscious state and to provide maximal clinical support with psychological and physical rehabilitation to allow for the possibility of full consciousness to develop.[1-3,7,8]

Some remarkable advances in the understanding of PVS and the minimal conscious state have occurred recently. Owen et al[9,10] assessed patients with disorders of consciousness, including PVS. For patients who retain motor function, behavioral testing supported by structural imaging and neurophysiological findings can measure accurately the patient's level of wakefulness and self-awareness. However, patients with no motor function can be extremely difficult to evaluate for level of consciousness and their cognitive abilities to perceive and understand commands. Owen et al[9,10] described a novel approach to this conundrum, using functional magnetic resonance imaging to demonstrate preserved conscious awareness in a patient fulfilling the criteria for a diagnosis of being in a vegetative state. Using functional magnetic resonance imaging, the authors showed that supplementary motor area activity during tennis imagery was identical in a patient diagnosed as being in a vegetative state and in a healthy volunteer. Furthermore, activity in the parahippocampal gyrus, posterior parietal lobe, and lateral premotor cortex in a PVS patient and in a healthy volunteer were also identical while imagining moving around a house. Thus, a patient in PVS who appears unaware of the environment and commands actually may be fully aware and cognitively intact but unable to show any response to stimuli. This is a major step forward in understanding the spectrum of PVS and also minimal conscious state cognitive abilities and the ethical and clinical needs to respect the patient's humanity and need for dignified care.

In 2007, Schiff et al[11] reported that a severely brain-injured patient in the minimal conscious state who underwent deep brain stimulation (DBS) showed significant behavioral improvement in attentiveness, recovery of spoken language and oral feeding, and in control of limb movements with central thalamic DBS.[11] This dramatic clinical response has provided a framework for future more comprehensive DBS interventions in a larger number of patients in the minimal conscious state and also PVS. It will be important to map thalamic nuclei to determine the responses to DBS that provide for improved alertness, language functions, and voluntary limb and facial movements. The thalamus is interposed between the brainstem and basal forebrain consciousness arousal systems. It is integrated into a reverberatory, reciprocal oscillatory loop activity with specific neuroanatomical connectivity with a broad representation of cerebral cortex involving multiple cognitive functions.[12,13] As pioneered by Schiff et al,[11] the defining and modulation of the structural and functional substrates of consciousness, of the human mind, of human thinking, and decision making represent a vital and dynamic new field for neuroscience.

In his 1994 book *The Astonishing Hypothesis*,[14] Crick opens with the following: "The Astonishing Hypothesis is that 'You', your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behavior of a vast assembly of nerve cells, and their associated molecules. As Lewis Carroll's Alice might have phrased it: 'You're nothing but a pack of neurons.' This hypothesis is so alien to the ideas of most people alive today that it can truly be called astonishing."[14] Crick's point, directly stated, is that there is no separate mind from the brain, the mind is the brain. Cartesian logic of a separate mind and brain is an archaic philosophical concept displaced by current functional magnetic resonance imaging, DBS studies, years of meticulous clinical-neuropathologic studies, and experimental neurophysiological animal studies that have proven that consciousness and mind are embedded into specific neuroanatomical arousal and behav-

ioral circuits. Crick is right that as astonishing as it may be to some, it is now clear that coma, consciousness, and cognition are neural-directed constructs and probably result from mathematical computations yet to be discovered.

Research into the causes of coma and the brain regions involved has moved ahead rapidly in the past 40 years since the publication of the *JAMA* classic article in 1968.[5] The longitudinal course of neurological diseases causal of coma often shows spontaneous improvement, and this is quantified using the neurological examination, imaging studies, clinical chemistries, and electroencephalographic monitoring. The future for therapy of chronic coma, chronic PVS, and the chronic minimal conscious state will require basic studies in neuroregeneration, growth factors, differentiation factors, neurogenesis, and synaptic reinervation. The neuromic program[15] for neuronal and glial differentiation will be essential for reproducing these molecular and structural events first in cell culture, in experimental animals with lesions causal of coma, and then applied to patients who are comatose. Stem cell research in which human adult skin cells are converted into induced pluripotential stem cells, differentiated into neurons or glia, and then differentiated to form neural circuits in vitro will be the first necessary step in bringing the technology of neuroregeneration from the bench to the bedside. These approaches will take time to develop, but they will be achieved and provide the means to treat patients who are comatose.

Financial Disclosures: None reported.

REFERENCES

1. Brust JCM. Coma. In: *Merritt's Neurology*. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:20-28.
2. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2): the Multi-Society Task Force on PVS. *N Engl J Med*. 1994; 330(22):1572-1579.
3. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology*. 2002;58(3):349-353.
4. Wijdicks EFM. The diagnosis of brain death. *N Engl J Med*. 2001;344(16): 1215-1221.
5. Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. A definition of irreversible coma: report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA*. 1968;205(6):337-340.
6. Joynt RJ. Landmark perspective: a new look at death. *JAMA*. 1984;252 (5):680-682.
7. Childs NL, Mercer WN. Late improvement in consciousness after posttraumatic vegetative state. *N Engl J Med*. 1996;334(1):24-25.
8. Giacino JT, Kalmar K. The vegetative and minimally conscious states; a comparison of clinical features and functional outcome. *J Head Trauma Rehabil*. 1997; 12(4):36-51. doi:10.1097/00001199-199708000-00005.
9. Owen AM, Coleman MR, Davis MH, et al. Detecting awareness in the vegetative state. *Science*. 2006;313(5792):1402.
10. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Using functional magnetic resonance imaging to detect covert awareness in the vegetative state. *Arch Neurol*. 2007;64(8):1098-1102.
11. Schiff ND, Giacino JT, Kalmar K, et al. Behavioral improvements with thalamic stimulation after severe traumatic brain injury [published correction appears in *Nature*. 2008;452(7183):120] Biondi, T [added]. *Nature*. 2007;448(7153): 600-603.
12. Parvizi J, Damasio AR. Neuroanatomical correlates of brainstem coma. *Brain*. 2003;126(pt 7):1524-1536.
13. Portas CM, Rees G, Howseman AM, Josephs O, Turner R, Frith CD. A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *J Neurosci*. 1998;18(21):8979-8989.
14. Crick FHC. *The Astonishing Hypothesis.* New York, NY: Charles Scribner's Sons; 1994.
15. Rosenberg RN. Neuromics and neurological disease. *Arch Neurol*. 2008; 65(3):307-308.