Executive Summary: A Review of the Literature on the Determination of Brain Death
Acknowledgements

The Planning Committee for the Forum on Severe Brain Injury to Neurological Determination of Death (April 9-11, 2003) commissioned this paper, a working draft, as a background information piece for Forum participants. This review of literature considers issues surrounding existing clinical practices in Canada. As an Executive Summary, it is an overview of recent medical literature on brain death and is abstracted from a longer, comprehensive paper on this topic prepared by Leonard Baron, MD (See final tab, workshop binder).

The views in the paper do not reflect the official policy of the Canadian Council for Donation and Transplantation and are not intended for publication in their current format.
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Introduction
Brain death is defined as irreversible loss of function of the brain, including loss of brainstem functional activity. The concept of brain death is a consequence of technologically medical intervention that modifies the clinical process of death. Generally, it is a widely accepted medical construct in the medical community and society at large. The concept of brain death has also been incorporated into many legal statutes worldwide.1

Despite this broad acceptance of the concept of brain death, inconsistencies in brain death determination persist. Some of these disparities are philosophical such as the debate about whole-brain formulation versus a brainstem formulation for brain death.2 Other inconsistencies persist in the clinical evaluation for brain death despite years of clinical research and experience with brain death determination.

Historical Perspective of Brain Death³
The mid-20th century saw the introduction of new technologies into the clinical care of the critically injured patient. It took little time for anecdotal evidence of never-before-described clinical conditions to appear in the medical literature. In a comprehensive work published in 1959, Mollaret and Goulon⁴ coined the term "le coma dépassé" meaning "a state beyond coma," which described patients in irreversible coma. This landmark paper addressed not only the clinical features of coma but also ethical issues and long-term outcomes in these patients.

The work of Mollaret and Goulon remained largely unrecognized in North America. In 1968, the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death⁵ was convened to “define irreversible coma as a new criterion for death.” This process led to the publication of the Harvard Criteria which was coincidentally published with an article on organ transplantation. The committee’s work, which was aimed at addressing the futility of care for patients who would inevitably die consequent to a catastrophic intracranial event, went generally unnoticed at the time. At nearly the same time, organ procurement for transplantation became an issue integrally related to brain death determination.

Refinements in the clinical determination of brain death such as the Minnesota Code of Brain Death Criteria by Mohandas and Chou⁶ were subsequently published. This article was the first to focus attention on irreversible brainstem damage in the evolution of brain death.

The notion of brainstem death was later refined by the Conference of Medical Royal Colleges and Faculties of the United Kingdom and was central to their published statement "Diagnosis of brain death"⁷ in 1976. Championed by Pallis and Harley, the brainstem formulation of brain death was formally adopted in 1995. It is noteworthy that prior to this, the brainstem formulation of brain death had been challenged in a BBC documentary that suggested that the criteria for the determination of brain death were inadequate and that patients were being declared brain dead for the purpose of organ retrieval for transplantation. The Royal College was charged with responding to these
claims and ultimately restored public confidence in the brainstem formulation of brain death prior to its formal adoption.

In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published guidelines for brain death determination. These guidelines recommended the use of "complementary diagnostic tests" to supplement the clinical examination in the diagnosis of brain death. The Commission also recommended that patients who had suffered ischemic hypoxic brain injury should be observed for no fewer than 24 hours before declaration of brain death. Notably, the President's Commission viewed its role as advisory; therefore, these guidelines were not intended for incorporation into the legal statutes of the day.

Additional refinements in the diagnosis of the brain injury and brain death have evolved since that time and, in 1995, the American Academy of Neurology published an evidence-based review of brain death. This guideline provides definitive affirmation that brain death is a clinical diagnosis. It goes on to clarify the role of supplementary testing in the diagnosis of brain death, especially in the presence of clinical confounding factors. This guideline ultimately became the foundation for many institutional guidelines on brain death in the United States.

Despite the general and longstanding acceptance of the concept of brain death in the medical community, legal support for the concept was lacking in the United States until the Uniform Determination of Death Act (UDDA) was passed. The UDDA forms the basis for brain death legislation in the United States. It accepts both the traditional circulatory formulation of death and the whole-brain formulation of brain death as acceptable criteria for death. Notably, it also states that determination of brain death should be made "in accordance with medical standards."

The Canadian Neurocritical Care Group Guidelines

In 1999, a subcommittee of the Canadian Neurocritical Care Group (CNCG) prepared new clinical practice guidelines for the diagnosis of brain death. These guidelines, which were largely similar to those published by the American Academy of Neurology, superceded earlier Canadian guidelines published in the Canadian Medical Association Journal in 1987 by the Brain Death Task Force.

According to the CNCG guidelines, the key elements required for the diagnosis of brain death include the following:

1) an established etiology capable of causing brain death in the absence of reversible conditions capable of mimicking brain death
2) deep coma with no response to deep stimulation
3) absent brainstem reflexes
4) apnea
5) reassessment after a suitable time interval
6) absence of confounding factors.

Two examinations were recommended to ensure that absence of brain function was persistent. The second examination also served to reduce the risk of error on initial evaluation. The CNCG guidelines stated that the interval time between examinations should vary depending upon the etiology of coma. Similar to other guidelines, the CNCG guidelines also recommended an observation period of 24 hours in the presence of
hypoxic-ischemic brain injury but provided only general recommendations for all other clinical applications.

**Whole-Brain Death versus Brainstem Death**

In the United States, the Uniform Determination of Death Act codifies the whole-brain formulation of brain death in stating that “an individual who has sustained ... irreversible cessation of all functions of the entire brain, including the brainstem, is dead.” This formulation is the one most commonly applied worldwide and forms the foundation for legal codification in most Western nations. A notable exception to this is the United Kingdom where the brainstem formulation of brain death is applied.12

The whole-brain formulation is characterized by irreversible loss of function of both the cerebral hemispheres and the brainstem. An intact brainstem is integral to the preservation of most regulatory and homeostatic mechanisms while the reticular formation, thalamus, and cerebral hemispheres all play roles in the preservation of consciousness. Global disruption of these structures forms the basis for whole-brain death.

It has been argued that laboratory evidence of retained hypothalamic-pituitary activity is inconsistent with the whole-brain formulation of brain death13. Bernat2 counters that persistent brain function may be evident in the context of integrative functioning, which is evaluated during clinical examination for brain death determination. He rejects laboratory evidence of cellular function, arguing that isolated cellular activity may persist in the absence of clinical signs of brainstem activity. Wijdicks14 provides a pathophysiologic explanation for preservation of hypophyseal-pituitary axis activity in brain death, noting that perfusion to these structures arises from extracranial vessels. Continued cellular activity may be a manifestation of retained blood flow to these nests of cells despite total intracranial cerebral circulatory arrest.

The brainstem formulation of brain death requires irreversible cessation of brainstem functioning. This formulation is based on the fact that the reticular formation forms the basis of consciousness and that the brainstem nuclei preserve regulatory and homeostatic mechanisms. Clinical evaluation of these structures in the context of brainstem death is essentially identical to that used for the evaluation of whole-brain death.

Clinical reports have documented focal pontine hemorrhage characterized by destruction of the brainstem with preservation of the thalamus and cerebral hemispheres. Bernat15 acknowledges that destruction of the brainstem and the reticular formation should result in unconsciousness. Nonetheless, he has argued against using the brainstem formulation because of the possibility of a ”super locked-in syndrome” in which awareness might be retained in the absence of all other signs of brainstem activity.

**Neurologic Determination of Death (NDD)**

The concept of brain death is broadly accepted in the mainstream medical community. Diagnosis is established by clinical examination, which may be substantiated by supplementary testing where confounding factors are identified.

A key objective of the current forum — Severe Brain Injury to Neurological Determination of Death — is to develop an evidence-based, “made-in-Canada” guideline for the diagnosis of brain death. With this in mind, it is proposed that the term “neurologic
determination of death” or “NDD” be applied to the process of establishing the diagnosis of brain death.

Inconsistencies in NDD

Who is most capable of performing NDD?
Most guidelines recommend that physicians involved in transplant activities be excluded from performing NDD. Some guidelines also exclude the primary attending physician, whereas others, such as those of the state of Florida, mandate that the primary physician must also be involved establishing brain death.16

Although it is widely recognized that NDD requires considerable clinical expertise, guidelines are inconsistent in designating those most suited to this purpose. While some guidelines and some statutes require evaluation by neurosciences specialists (i.e. neurology or neurosurgery), most guidelines defer to any physician with suitable training and clinical experience.

Although appropriately trained to perform the task, practicing neurosciences specialists may have limited experience in NDD. Any number of medical specialists may provide care for the brain-injured patient in the intensive care environment, including anesthesiologists, surgeons, pediatricians, and internal medicine specialists. It is intuitive that any of these individuals would be rational choices to perform NDD-related activities; this position is consistent with the views of both Wijdicks17 and Pallis and Harley18

How many examinations are recommended when performing NDD?
Most clinical guidelines require two examinations by a single practitioner performed within an appropriate wait interval (see below: “What is an appropriate time interval …?”). The CNCG guideline addresses this issue in describing re-examination to eliminate errors in clinical evaluation and to document persistent non-functioning of the brain.

Other guidelines such as those of the Australia and New Zealand Intensive Care Society19 (ANZICS) stipulate mandatory certification of brain death by two practitioners whenever organ procurement for transplantation is being considered. Where explantation is not a consideration, a single practitioner may provide certification of brain death. Nonetheless, ANZICS recommends that certification of brain death should be provided by two physicians in all instances.

There is no literature evidence to suggest that evaluation by two physicians is preferable or superior to that of a single clinician from a clinical perspective.

What are the minimum clinical standards for the determination of brain death?
Requirements for the substantiation of brain death are noticeably similar among various guidelines. The clinical examination should document the following criteria and conditions:

1) deep unresponsive coma
2) absent motor responses
3) absence of pupillary responses to light; pupils at mid-position, greater than 4 mm dilated
4) absent corneal reflexes
5) absent vestibulo-ocular response
6) absent gag reflex
7) absent cough in response to tracheal suctioning
8) absent sucking and rooting reflexes
9) apnea

Although not included in the clinical criteria for brain death, the oculocephalic (doll’s eye) reflex is frequently mentioned in the literature. Ashwal\textsuperscript{20} recommends that the oculocephalic reflex be examined in neonates and infants where vestibulo-ocular reflexes may be more difficult to illicit. Wijdicks\textsuperscript{17} describes the clinical examination for ocular movements. He suggests that the oculocephalic reflex may lack sensitivity in confirming absent ocular movement in adults. The United Kingdom code fails to mention the oculocephalic reflex but examination for this reflex is recommended by Pallis and Harley\textsuperscript{21}. A positive response is clear indication that the brainstem is functional and that further examination for NDD is not warranted.

Clinical examination may be limited by the nature of injuries sustained by the patient. In such instances, supplementary testing is recommended.

**What apneic thresholds should be used in NDD?**
North American guidelines usually recommend an apneic threshold $\text{PaCO}_2 \geq 60 \text{ mm Hg}$ determined by arterial blood gas analysis. In contrast, the United Kingdom code requires documentation of apnea with a threshold $\text{PaCO}_2 \geq 50 \text{ mm Hg}$.

Some guidelines also recommend documentation of an acidemic pH $< 7.28$ although no evidence-based source for this recommendation could be identified.

**What minimum temperature threshold should be required for establishing NDD?**
Recommended minimum temperature thresholds vary from $32.2^\circ\text{C}$ to $36.5^\circ\text{C}$ in published guidelines. There is no evidence-based support for any particular temperature threshold.

Although there is a poor correlation between level of consciousness and core temperature,\textsuperscript{22} neurologic function generally diminishes as hypothermia becomes more pronounced. Hyporeflexia is frequently seen at temperatures less than $32^\circ\text{C}$ and areflexia may ensue when core temperatures less than $28^\circ\text{C}$ are seen.\textsuperscript{23}

Many guidelines refer specifically to minimum core temperature requirements for NDD. However, methods of temperature measurement are seldom specified and, where they are, not all are indicative of true core temperature.

**What is an appropriate time interval between successive examinations for NDD?**
It is commonly stated that interval time depends on the etiology of brain injury. The literature is relatively consistent in recommending a minimum 24-hour observation period for patients suffering from hypoxic-ischemic brain injury. In spite of this consistency, there is no scientific corroboration for this recommendation which dates back to the era of the President’s Commission.

The interval time has decreased since the early recommendations of the Ad Hoc Committee of the Harvard Medical School. More recently, the CNCG guidelines recommended wait intervals ranging from 2 to 24 hours depending on the etiology of brain injury. Specific recommendations were otherwise absent. Variable interval times for examination have also been recommended based upon patient age\textsuperscript{24} (see below: “Should clinical criteria be modified on an age-related basis?”). A literature review could not establish a firm basis for recommended interval times.
**Should clinical criteria be modified on an age-related basis?**

The CNCG guidelines state that the adult clinical criteria may be applied to pediatric patients with a post-conceptional age of greater than 52 weeks and clinical examination alone may be insufficient in children younger than this age. Other guidelines recommend specific age-related thresholds for the application of adult clinical criteria in the determination of brain death. Most commonly, it is recommended that adult criteria may be used over the chronological age of 2 months.

Many guidelines offer differing recommendations for various age groups. For example, Ashwal recommends that infants up to 2 months of age be examined on two occasions, 48 hours apart, and that infants from 2 months to 1 year be examined on two occasions, 24 hours apart. Supplementary EEG testing should be considered. For infants over one year of age, two examinations spaced 12 to 24 hours apart should be performed while supplementary testing is optional.

These recommendations are largely similar to those of the American Academy of Pediatrics Task Force on Brain Death in Children with the exception that EEGs were definitively recommended by the Academy.

The age limits for the application of adult brain death guidelines in children and the requirements for supplementary testing vary between guidelines. Canadian investigators, Farrell et al., have indicated that the clinical history, physical examination, and an apnea test are sufficient in diagnosing pediatric brain death without the use of supplementary testing. Age-based modifications of observation times, interval times and indications for supplementary testing in children are inconsistent and without clear scientific basis. This literature review found that there is little, if any, evidence to support many of the age related recommendations quoted in the literature.

**What is the role of supplementary testing in establishing NDD?**

NDD is a clinical diagnosis. Provided that a definitive etiology for brain death is established, irreversibility is confirmed in the absence of confounding clinical factors and all clinical criteria for NDD are met, further supplementary testing is neither required nor recommended. Brain death should never be considered present when there is any evidence of brainstem reflex activity, motor response, or signs of respiratory activity.

In North America, the role of supplementary testing relates primarily to those situations where full clinical examination cannot be completed because of the nature of the injuries (e.g. ocular trauma and middle ear injury) or situations where co-existing diseases such as endocrine or metabolic disturbances are identified. Confounding clinical conditions such as hypothermia, drug intoxication, or drug therapy must be either treated, excluded, or allowed to dissipate before NDD.

Currently, cerebral angiography and Tc-99m hexamethylpropylene-amine oxime (Tc-99m HMPAO) radionuclide angiography are the only supplementary diagnostic tests that evaluate whole brain blood flow. Consequently, these are also the only tests capable of identifying cerebral circulatory arrest consistent with the current conceptual understanding of brain death.

**How does persistent spinal reflex activity affect NDD?**

Reflex spinal activity is identified in a significant proportion of patients who are diagnosed with traditional brain death criteria. Spinal activity has been documented in cases where cerebral circulatory arrest is radiologically proven and where
electrocerebral silence is demonstrated on EEG. Activity may range from subtle finger jers to the more complex “Lazarus sign.”

Persistence of spinal reflexes is considered compatible with neurologically determined brain death. More complex reflex activity may cause diagnostic confusion in some cases and may be of a nature that an experienced clinician may question the diagnosis of brain death. Supplementary testing may aid in resolving this issue.

**How is NDD modified for drug intoxication?**

Drug effects can arise either from therapeutic drug administration or from non-therapeutic drug ingestion by the patient. Knowledge of the pharmacology of therapeutic drugs allows physicians to determine rational periods of observation before NDD.

Drug screening may identify self-administered agents capable of producing coma-like states. Where the identity of ingested agents can be reasonably established and measured concentrations of the agent are sub-therapeutic, NDD may proceed. Otherwise, an observation period extending over four half-lives of the agent is advised before NDD. This recommendation is based on theoretical pharmacologic considerations rather than evidence-based clinical studies.

Where identity of the toxin cannot be established, a 48-hour observation period is recommended. If, after this period, clinical examination is compatible with neurologic brain death, supplementary testing is recommended to verify cerebral circulatory arrest.

**At what point during NDD is a patient legally dead?**

The medical literature is relatively silent on this issue. NDD requires a minimum of two clinical examinations by one medical practitioner. If the patient proceeds to organ donation, hours may pass before ventilatory and resuscitative measures are withdrawn.

Pallis argues that the patient may be declared dead once the findings of the clinical examination are consistent with brain death. At this point, he states that the patient becomes a “ventilated cadaver.” It is unclear whether Pallis considers the time of death to be the time of the first or the second examination for NDD.

Wijdicks does not appear to address this specific issue but he does state that, in experienced hands, the result of a second examination has been invariably consistent with the initial examination and that performance of a second formal apnea test is not required. From these statements, it may be reasonable to designate the time of death as the time of the first examination for NDD.

**References**

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