References

1 *Organs for Transplants. A Report from the Organ Donation Taskforce*. London: Department of Health, 2008. Available from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082122

2 Farsides B. Respecting wishes and avoiding conflict: understanding the ethical basis for organ donation and retrieval. *Br J Anaesth* 2012; **108** (Suppl. 1): i73–i79

3 Price D. Legal framework governing deceased organ donation in the UK. *Br J Anaesth* 2012; **108** (Suppl. 1): i68–i72

4 Saunders J. Bodies, organs and saving lives: the alternatives. *Clin Med* 2010; **10**: 26–9

5 Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. *Br J Anaesth* 2012; **108** (Suppl. 1): i108–i121

6 Academy of Medical Royal Colleges. A Code of Practice for the Diagnosis and Confirmation of Death. 2008. Available from http://www.aomrc.org.uk/publications/reports-guidance.html

7 Mental Capacity Act 2005 and associated Code of Practice. ISBN 0 10 560905 6. Available from http://www.justice.gov.uk/guidance/protecting-the-vulnerable/mental-capacity-act/index.htm (accessed 23 September 2011)

8 Adults with Incapacity (Scotland) Act. 2000. Available from http://www.scotland.gov.uk/Publications/2006/03/07090322/0 (accessed 23 September 2011)

9 *Liverpool care pathway for the dying patient (LCP)*. Marie Curie Palliative Care Institute. Available from http://www.mcpcil.org.uk

10 Randhawa G. Death and organ donation: meeting the needs of multiethnic and multifaith populations. *Br J Anaesth* 2012; **108** (Suppl. 1): i88–i91

British Journal of Anaesthesia **108** (S1): i6–i9 (2012)
doi:10.1093/bja/aer355

EDITORIAL III

Brain death: time for an international consensus

M. Smith

Department of Neurocritical Care, The National Hospital for Neurology and Neurosurgery, University College London Hospitals, Queen Square, London WC1N 3BG, UK

E-mail: martin.smith@uclh.nhs.uk

Death is the great certainty of life—its inevitable end. In this issue of the journal, Gardiner and colleagues[1] present a comprehensive review of the history and current status of the diagnosis of death, and discuss the determination of death by neurological criteria (brain death) in some detail. Although it is more than 40 yr since the concept of brain death was first introduced into clinical practice, many of the controversies that surround it have not been settled. These include the relationship between brain death and death of the whole person, the international differences in the nomenclature and criteria for the determination of brain death, and the inextricable links between brain death and organ donation.

The concept of brain death emerged during the 1950s when, as a consequence of developments in critical care, clinicians were faced for the first time with the prospect of an apparently 'alive' patient sustained by mechanical ventilation long after brain function had ceased. The development of organ transplantation and the associated need to determine death before organ retrieval led to the publication of the first widely accepted standard for the confirmation of brain death by an *ad hoc* Committee of the Harvard Medical School in 1968.[2] Although this early link with organ donation might give the impression that brain death was a construct designed only to facilitate donation, this is incorrect. Most importantly, the confirmation of brain death allows the withdrawal of therapies that can no longer conceivably benefit an individual who has died.

In the UK, a Conference of the Medical Royal Colleges and their faculties produced guidance for the diagnosis of brain (stem) death in 1976[3] and, in a subsequent memorandum 3 yr later, equated brain death with death of the whole person for the first time.[4] In the USA, the 1981 Uniform Determination of Death Act (UDDA) gave equivalence to death determined by neurological and cardiovascular criteria, although it did not mandate a standard by which brain death should be determined, confirming only that this should be in accordance with accepted medical standards.[5] There is broad consensus, particularly in Western cultures, that human death is ultimately death of the brain and that this crucially involves the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe.[5] Taken together, these elements represent the most basic manner in which a human being can interact with their environment. Confusingly though, brain death is defined in two different ways based on 'whole' brain and 'brainstem' formulations. The UDDA relies on the whole-brain formulation and states that 'an individual who has sustained irreversible cessation

of all functions of the entire brain, including the brain-stem, is dead'.[5] This forms the standard for the determination of death by neurological criteria in the USA and most European countries and is based, in theory at least, on confirmation of the loss of *all* brain function including, but not limited to, the brainstem. Unlike whole-brain death, the diagnosis of brainstem death, such as that used in the UK, does not require confirmation that *all* brain functions have ceased, rather that none of those functions that might persist should indicate any form of consciousness.[6] The determination of brainstem death requires confirmation of the 'irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe' and relies on the fact that key components of consciousness and respiratory control, the reticular activating system and nuclei for cardiorespiratory regulation, reside in the brainstem.[3]

Despite the apparent differences, the *clinical* determination of whole-brain and brainstem death is identical, although the role of confirmatory investigations is different. Patients with preserved cortical electrical activity or intracranial blood flow can be considered to be dead in countries that utilize a brainstem approach but not in those where a whole-brain concept is applied. Thus, it has been argued that brainstem death has a lower burden of proof than whole-brain death and that it cannot exclude the retention of awareness in the absence of all other signs of brainstem activity.[7] Equally, the diagnosis of whole-brain death can be viewed as an 'approximation' because the irreversible loss of *all* intracranial neurological functions is not confirmed during its clinical determination, and some functions, such as neuroendocrine (hypothalamic–pituitary) responses, are maintained after brain death. Supporters of the whole-brain concept argue that the persistence of isolated cellular activity of the neuroendocrine axis in the absence of brainstem activity is irrelevant and, in any case, can be explained by its extracranial blood supply.[7]

Although the determination of death by neurological criteria meets with widespread public and professional acceptance, the relationship between death of the brain and the death of the individual continues to be misunderstood.[8] Notwithstanding the legal and societal importance of identifying the actual moment of a person's death, death is not a single event but a process that leads progressively to the failure of all functions that constitute the life of the human organism.

Pragmatically, once a threshold of irreversibility has been reached (and brain death is such a point), it is not necessary to wait for the death of the whole organism for the inevitable consequence of its biological death to be certain. However, the concept that death is a process, but one that can nevertheless be determined at a particular moment in time, is not widely appreciated and this leads to misunderstanding by both the public and professionals.[8] Reports of brain-dead patients being 'kept alive on a ventilator' are familiar. There have also always been individuals and whole societies that do not accept under any circumstances that brain death equates to the death of the individual. Some suggest that it is dishonest to make this claim,[9] whereas others point out that the biological death of the whole human organism cannot (and is not required to) be proven during the diagnosis of brain death.[10]

Initially, it was argued that brain death equates to the death of the individual because, after brain death, the body ceases to be an integrated organism and rapidly becomes a disintegrating collection of organs which have permanently lost the capacity to work as a coordinated whole.[10 11] However, it is now clear that brain-dead patients can show levels of somatic integration that may persist for some time.[12] An alternative concept, a 'loss of personhood', has therefore been suggested as the rationale for the neurological determination of death. Here the loss of certain key human functions (such as the ability to be conscious or apply reason) is sufficient for the philosophical and ethical justification of a diagnosis of death. It is also consistent with the legal determination of the death of a person even if they occur independently from the death of the whole organism.[10]

While the 'loss of personhood' concept resonates with the whole-brain formulation of brain death, it does risk giving the impression that brain death is somehow a less rigorous determinant of death than a cardiovascular standard and it has not found widespread support. The ongoing concerns with a model of brain death that relies on a loss of somatic integration led the US President's Council on Bioethics to propose a new unifying concept of death in 2008. The Council concluded that it is the 'ability to conduct the vital work of a living organism—the work of self-preservation, achieved through the organism's need-driven commerce with the world' that supports the continued use of brain death as a valid determinant of human death.[13] The Council also reiterated its support for a whole-brain formulation and rejected a reliance on brainstem death, arguing that the inner state of a person with residual cortical activity in the complete absence of brainstem activity is unknown. However, the associated proposal that 'total brain failure' should replace the traditional term 'whole brain death' may be viewed as unhelpful. Intensivists are accustomed to supporting other 'failing' vital organ systems to recovery and any suggestion that 'total brain failure' is reversible misrepresents the fundamental principles of brain death.

The criteria for the determination of brain death are robust. There are no published reports of recovery of neurological function after a diagnosis of brain death using the criteria given in the 1995 American Academy of Neurology practice parameter.[14] It is therefore surprising, and of some significant concern, that deviation from this practice guideline is relatively widespread.[15] Recent reports describing the apparent 'reversibility' of brain death have been refuted because of failure to adhere to such standard guidelines.[16–18] In one report, the authors appear to dismiss the potential confounding effects of a very high cumulative

dose of fentanyl in a patient with renal and hepatic impairment who had recently suffered a cardiac arrest and been treated with hypothermia.[17] This case illustrates the absolute imperative of meticulous attention to conformation with published guidance during the determination of brain death, not only in the conduct of the clinical examination but also, and possibly more importantly, in the confident exclusion of confounding factors. Although the authors agreed in subsequent correspondence that there is no 'reversible' brain death, this case has re-ignited the debate about the nature of brain death.[18 19]

Despite general consensus on the concept of brain death, there are major international differences in its diagnosis.[1 20] The majority of countries have followed the lead of the USA and the UK in specifying that the *clinical* diagnosis of brain death is sufficient for the determination of death in adults. While there is unanimity that confirmation of the absence of brainstem reflexes is fundamental to the clinical determination of brain death, there are wide variations in the requirements for the conduct of the apnoea test. Fewer than 60% of jurisdictions include induced hypercarbia to a specified Pa_{CO_2} target (and confirmation with arterial blood gas analysis) in their guidance. Others only stipulate disconnection from the ventilator for a defined period or provide no guidance for the conduct of the apnoea test.[20] This is concerning because the confirmation of apnoea is fundamental to the determination of brain death (either whole brain or brainstem) and this can only be assured if the degree of acute hypercarbia is sufficient to stimulate the respiratory centre.

Whatever standard is used to determine brain death, 'irreversibility' is usually not defined and relies in practice on repeated assessment over time. A second clinical examination is required in many countries and this was presumably introduced to minimize the likelihood of errors in diagnosis. However, while there is no convincing evidence that a second test is necessary, there is evidence that it delays the determination of brain death. This leads to the loss of viable organs for donation and substantial additional intensive care costs.[21] A second apnoea test is not required in some countries that mandate two clinical examinations, but omission of this crucial component from one of the examinations is illogical. The mandated time interval between the two examinations also varies. While a 24 h period is usual after hypoxic–ischaemic brain injury, there is generally less specific guidance for other clinical circumstances.

Some brain death guidelines specify the qualification and level of experience of those determining death, and most explicitly exclude anyone involved in organ transplantation.[20] The number of doctors required to determine brain death also varies widely, although most commonly a single doctor is sufficient. Two doctors (the UK standard) are required in only around one-third of countries. Some jurisdictions mandate that two different doctors must determine brain death only when organ transplantation is being considered, but this is confused thinking since the determination of death should be the same whether or not organ donation is a likely outcome. Brain death documentation is also highly variable, with reports of key components of the clinical examination being omitted in almost half of cases.[22] Whether this is a problem of documentation or a more concerning failure to conduct a full clinical examination is unclear.

Confirmatory tests are optional in most countries and reserved for circumstances where some doubt exists about the clinical diagnosis of brain death (e.g. after infusion of long-acting sedative drugs such as thiopental) or because the patient might be too unstable to undergo an apnoea test.[20 23] Confirmatory investigations generally fall into two general categories. These either demonstrate the loss of electrical activity of the brain or confirm the absence of intracerebral blood flow.[24] A recent UK survey found that more than 50% of neuroscience centres are confident in relying on ancillary tests to confirm brain death where there is doubt about the clinical diagnosis, but that there is considerable variation in opinion and practice with regard to the application of such tests, particularly after sedative drug infusion.[25] It is likely that this variation is greater outside neuroscience units where many of the ancillary tests, and personnel to interpret them, are either unavailable or used infrequently. Confirmatory tests are not specifically recommended in current UK guidance and it is time for a broad debate on the role, type, and application of ancillary tests and publication of consensus guidance that has professional support.

Although the juxtaposition of brain death and organ donation may often be inevitable, it can also be unhelpful. It is inevitable, but also correct, because a diagnosis of brain death allows a patient who wishes to donate their organs after death to have that wish respected and their gift maximized. It is unhelpful because of an increasingly prominent view that the diagnosis of brain death is relevant only in the context of potential organ donation. A person should be declared (brain) dead because he or she is in fact dead, rather than because of any potential for organ donation. In this way, the professional and legal acceptability of withdrawal of treatment (including mechanical ventilation) which is merely prolonging somatic function can be assured. The recently updated Code of Practice in the UK has separated completely the diagnosis and confirmation of death from issues surrounding organ donation and this is helpful.[6] However, it should not be forgotten that organ donation is a key component of end-of-life care in appropriate patients and that, crucially, it should be considered in all those who are brain dead.

Despite the fact that the concept of brain death was introduced more than 40 yr ago, many people continue to struggle with both its concept and justification. Although guidelines are available in many countries to standardize national processes for the diagnosis of brain death, the current variation and inconsistency in practice make it imperative that an international consensus is developed. As a minimum, this should clarify the criteria for the determination

of brain death and provide specific instructions about the clinical examination necessary and the conduct of the apnoea test. It should also stipulate the role and type of confirmatory investigations, identify the training and experience of those able to determine death by neurological criteria, and detail the required level of documentation. This is likely to require the UK to reconsider its reliance on the brainstem formulation of brain death, but this should not prevent us from enthusiastically embracing the debate. An international consensus on the determination of brain death is desirable, essential, and long overdue.

Acknowledgement

I am grateful to Sandra Fairley and Amanda Gibbon for reviewing the manuscript.

Declaration of interests

M.S. is partially funded by the Department of Health's National Institute for Health Research Centres funding scheme via the UCLH/UCL Comprehensive Biomedical Research Centre. The opinions expressed in this article are the author's own.

References

1 Gardiner D, Shemie S, Manara A, Opdam H. International perspective on the diagnosis of death. *Br J Anaesth* 2012; **108** (Suppl. 1): i14–i28

2 A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. *J Am Med Assoc* 1968; **205**: 337–40

3 Diagnosis of brain death. Statement issued by the honorary secretary of the Conference of Medical Royal Colleges and their faculties in the United Kingdom on 11 October 1976. *Br Med J* 1976; **2**: 1187–8

4 Diagnosis of death. The Conference of Medical Royal Colleges and their faculties in the UK. *Lancet* 1979; **313**: 261–2

5 *Uniform Determination of Death Act*. Available from http://www.law.upenn.edu/bll/archives/ulc/fnact99/1980s/udda80.pdf (accessed 5 September 2011)

6 A code of practice for the diagnosis and confirmation of death. Academy of the Medical Royal Colleges, London, 2008. Available from http://www.aomrc.org.uk/reports-guidance.html (accessed 5 September 2011)

7 Baron L, Shemie SD, Teitelbaum J, Doig CJ. Brief review: history, concept and controversies in the neurological determination of death. *Can J Anaesth* 2006; **53**: 602–8

8 Souter M, Van NG. Ethical controversies at end of life after traumatic brain injury: defining death and organ donation. *Crit Care Med* 2010; **38**: S502–9

9 Hill DJ. Diagnosing brain death. Honesty is the best policy. *Br Med J* 2002; **325**: 836

10 Zamperetti N, Bellomo R, Defanti CA, Latronico N. Irreversible apnoeic coma 35 years later. Towards a more rigorous definition of brain death? *Intensive Care Med* 2004; **30**: 1715–22

11 Pallis C. Whole-brain death reconsidered—physiological facts and philosophy. *J Med Ethics* 1983; **9**: 32–7

12 Shewmon DA. Chronic 'brain death': meta-analysis and conceptual consequences. *Neurology* 1998; **51**: 1538–45

13 The President's Council on Bioethics. Controversies in the determination of death: a white paper of the President's Council on Bioethics 2008. Washington, DC, 2008. Available from http://bioethics.georgetown.edu/pcbe/reports/death/Controversies%20in%20the%20Determination%20of%20Death%20for%20the%20Web%20%282%29.pdf (accessed 5 September 2011)

14 Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2010; **74**: 1911–8

15 Greer DM, Varelas PN, Haque S, Wijdicks EF. Variability of brain death determination guidelines in leading US neurologic institutions. *Neurology* 2008; **70**: 284–9

16 Roberts DJ, MacCulloch KA, Versnick EJ, Hall RI. Should ancillary brain blood flow analyses play a larger role in the neurological determination of death? *Can J Anaesth* 2010; **57**: 927–35

17 Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. *Crit Care Med* 2011; **39**: 1538–42

18 Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. There is no reversible brain death. *Crit Care Med* 2011; **39**: 2204–5

19 Webb A, Samuels OB. There is no reversible brain death. *Crit Care Med* 2011; **39**: 2206

20 Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology* 2002; **58**: 20–5

21 Lustbader D, O'Hara D, Wijdicks EF, *et al.* Second brain death examination may negatively affect organ donation. *Neurology* 2011; **76**: 119–24

22 Wang MY, Wallace P, Gruen JP. Brain death documentation: analysis and issues. *Neurosurgery* 2002; **51**: 731–5

23 Wijdicks EF. The clinical criteria of brain death throughout the world: why has it come to this? *Can J Anaesth* 2006; **53**: 540–3

24 Young GB, Shemie SD, Doig CJ, Teitelbaum J. Brief review: the role of ancillary tests in the neurological determination of death. *Can J Anaesth* 2006; **53**: 620–7

25 Sherrington A, Barrass L, Mandersloot G, Healy M. A survey on the use of ancillary tests in the diagnosis of brain stem death. *J Neurosurg Anesthesiol* 2011; **23**: 286