The Signs of Death
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SURVIVING AREAS OF BRAIN TISSUE IN BRAIN DEATH: IS THE WHOLE MORE THAN THE SUM OF ITS PARTS?*

MICHAEL G. HENNERICI

Introduction

In a recent review published in *Nature Neuroscience* (2005) Steven Laureys updated the conflict of death and diagnosis of brain death, which has evolved since the invention of the positive pressure mechanical ventilator by Bjorn Ibsen in the mid 1950s and its widespread use in intensive care units (ICU) in the 1960s: patients with severe primary or secondary brain damage who otherwise died within hours or a few days from failure of neuroendocrine and homeostatic regulation, circulation and respiration, could have their heart beat and systemic circulation provisionally sustained and with nowadays refined ICU technology, even deliver a mature child artificially. Until that time of technological progression such patients had died from

TABLE 1. MILESTONES IN DEATH AND DYING DEFINITIONS

1952 Bjorn Ibsen invented mechanical ventilation
1957 Pope Pius XII ruled that there is no obligation to use extraordinary means to prolong life in critically ill patients
1959 Mollaret & Goulon coined the term „coma dépassé“ and defined death on the basis of neurological criteria
1968 Harvard MedSchool AdHocCommittee defined irreversible coma as new criterion for death
1976 Conference of Medical Royal Colleges and their Facilities in the UK defined *Diagnosis of brain death*
1982 C. Pallis ABS of *Diagnosis of brain stem death*
1995 AAN Practice parameters for determining brain death in adults

* 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.

apnea in line with the traditional and ancient cardio-respiratory-centric diagnosis, which has turned on to a neurocentric diagnosis of death.

Although the majority of people around the world, when asked, declared death by cardiopulmonary criteria (>86%), i.e. when cardiac functions cease, versus the concept of brain death (9%), the latter has been accepted and legally used in many countries since the mid seventies of the last century for specific conditions, based on strict definitions and standardised diagnostic formulations as proposed.

TABLE 2. A DEFINITION OF IRREVERSIBLE COMA

There are two reasons why there is a need for a definition: (1) Improvements in resuscitative measures have led to save those who are desperately injured. Sometimes these efforts have only partial success so that the result is an individual whose heart continues to beat but whose brain is irreversibly damaged. ... (2) Obsolete criteria for the definition of death can lead to controversy in obtaining organs for transplantation....

(Ad hoc Committee of the Harvard Medical School to examine the definition of brain death, JAMA 1968;205:pp. 85).

TABLE 3. CHARACTERISTICS OF IRREVERSIBLE COMA

1. unreceptivity and unresponsitivity
2. no movements or breathing
3. no (cranial) reflexes
4. flat electroencephalogram

(Ad hoc Committee of the Harvard Medical School to examine the definition of brain death, JAMA 1968;205:pp. 85).

Brain Death Formulations

Roughly the human brain consists of two hemispheres, the dominant and the non-dominant one, the basal ganglia including the thalamus, the cranial nerves including the retina of the eyes, the pituitary gland, the brain stem and the cerebellum (Figure 1, see page 426).

The *whole-brain formulation* states that an individual who has sustained irreversible cessation of all functions of the entire brain, including the brain stem, is dead. This formulation is the most commonly applied worldwide and forms the foundation of legal qualification in many Western nations. It is characterised by irreversible loss of function of both supra- and infratentorial brain territories with the brain stem being integral to the preservation of most regulatory and homeostatic mechanisms, while in particular, thalamus and cerebral hemispheres play important roles in the preservation of consciousness. Global disruption of these structures forms the basis for the *whole-brain* formulation of death.

A notable exception from this definition exists in the United Kingdom, where *the brain stem death formulation* was originally promoted, because people thought that 'irreversible loss of the capacity for consciousness combined with irreversible loss of the capacity to breathe' was the more correct term of death irrespective of whether this condition was induced by intracranial events or by extracranial phenomena, and irrespective of a combined supra- and infratentorial or infratentorial lesion only, the latter invariably heralding asystole. Data, although sparse, showed convincingly that indeed asystole developed within days after the diagnosis of brain stem death.

Practically that means that clinical testing is identical for both *whole-brain death*, and *brain stem death* formulations of brain death. Both represent the same pathophysiology, e.g. irreversible cessation of brain stem function. However, as patients with a primary lesion affecting the brain stem *only* may have supratentorial parts of the brain still active, this condition requires – according to diagnostic regulations in many countries – additional technical studies to support the persistent absence of supratentorial *brain perfusion* and absence of *electrical activity during* EEG recordings.

Christopher Pallis anticipating criticism wrote in his early book, *ABC of Brain Stem Death, From Brain Death to Brain Stem Death (1982), British Medical Journal*:

> Judicial hanging is another cause of lethal, primary brain stem injury. Death in such cases is widely believed to be due to a fracture-dislocation of the odontoid, with compression of the upper two segments of the spinal cord. Although such a lesion may be found in some cases,

> Professor Simpson, Home Office Pathologist when capital punishment was still resorted to in the UK, has told me (Christopher Pallis) that a rupture of the brain stem (between pons and medulla) was more common.
>
> In judicial hanging respiration stops immediately, because of the effect of the brain stem rupture on the respiratory centre. The carotid or vertebral arteries may remain patent. The heart may go on beating for 20 minutes. Circulation continues, and parts of the brain are probably irrigated with blood (or diminishing oxygen saturation) for several minutes. I would guess that an electroencephalogram might for a short while continue to show some activity, despite the mortal injury to the brain stem. *Is such an individual alive or dead?* The very posing of such a question forces one to focus attention on the reversibility or irreversibility of the brain stem lesion and away from extraneous considerations.

Some have continuously argued against using the brain stem formulation for other reasons, e.g. because of the possibility of 'a super-locked-in-syndrome', in which awareness might be retained in the absence of all other signs of brain stem activity. Laboratory evidence has also been used, suggesting that retained hypothalamic pituitary or isolated cellular activity, may reflect, despite absence of clinical signs of function, subtotal brain death (noting that perfusion of all these structures arises from extracranial vessels only). To understand this better I would like to briefly review the different states of condition after acute brain injury resulting in similar but not identical clinical presentation of comatose patients and to present an example from our department. Doing this I will try to avoid, inasmuch as possible, overlap with what has already been reviewed during this symposium.

The history of brain death definitions from former definitions of death was reviewed by Robert B. Daroff and the changes and modifications in procedures to determine brain death around the world were discussed by Eelco F.M. Wijdicks. In addition, Conrado J. Estol clearly strengthened the differences in diagnosis and prognosis of patients with unconsciousness and coma after acute brain injury, who suffered from (i) *locked-in syndrome* (a term coined by Fred Plum and Jerome Posner) (1966), (ii) *the vegetative state*, similarly introduced by Bryan Gennett and Fred Plum (1972) and (iii) *brain death.* This is essential in order not to misdiagnose and mix these entities with brain death for medical, philosophical, legal and ethical issues, and to avoid wrong definitions and formulations. The tragic death of Terri Schiavo illustrated the world's difficulties that surround death in the vegetative state, as many journalists and even authorities inaccurately referred to Schiavo's condition as 'brain death'.

Our patient was an 83-year-old man, admitted for progressive right sensorimotor hemiparesis, resulting from left paramedium pons infarction, due to moderate basilar artery stenosis (Figure 2).

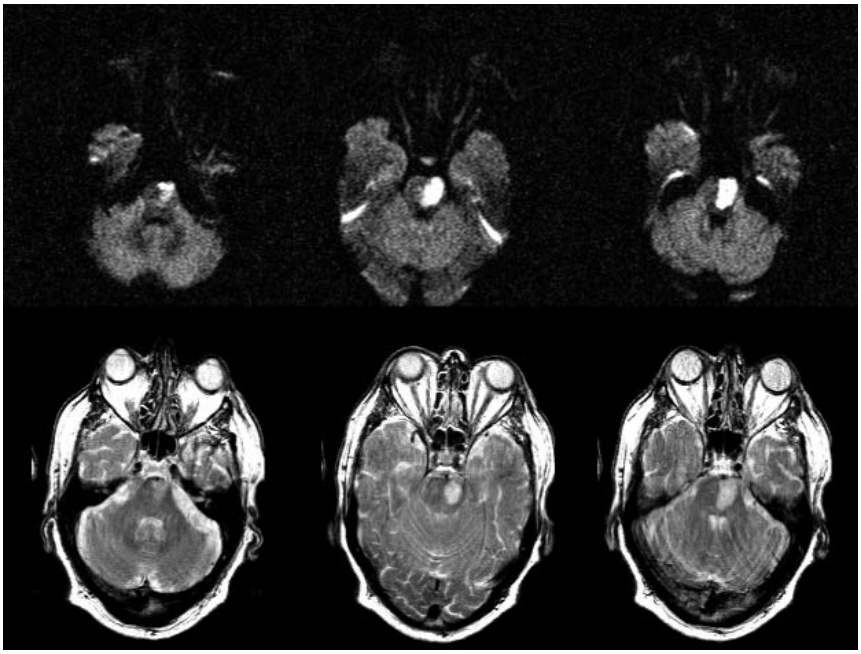

Figure 2. Patient (83 years, male) admitted for progressive right sensori-motor, hemiparesis due to a left paramedian pons infarction in presence of moderate basilar artery stenosis.

About two weeks later he suddenly deteriorated and suffered from quadriplegia, dysphagia, anarthria, and presented bradycardia during vagal stimulation on treatment and finally became comatose. This was caused by a second right acute pontine infarction and persisted for another two weeks. The patient was neither intubated nor artificially ventilated and died finally from renal failure and sepsis (Figure 3).

As you can see this patient, with a typical locked-in syndrome, did not develop, at any time of his illness, signs of *brain stem* or *whole-brain death*. However, had he been artificially ventilated and basilar artery thrombosis progressed, producing all signs requested for the diagnosis of brain stem death, this situation might have occurred, despite preservation of supra-

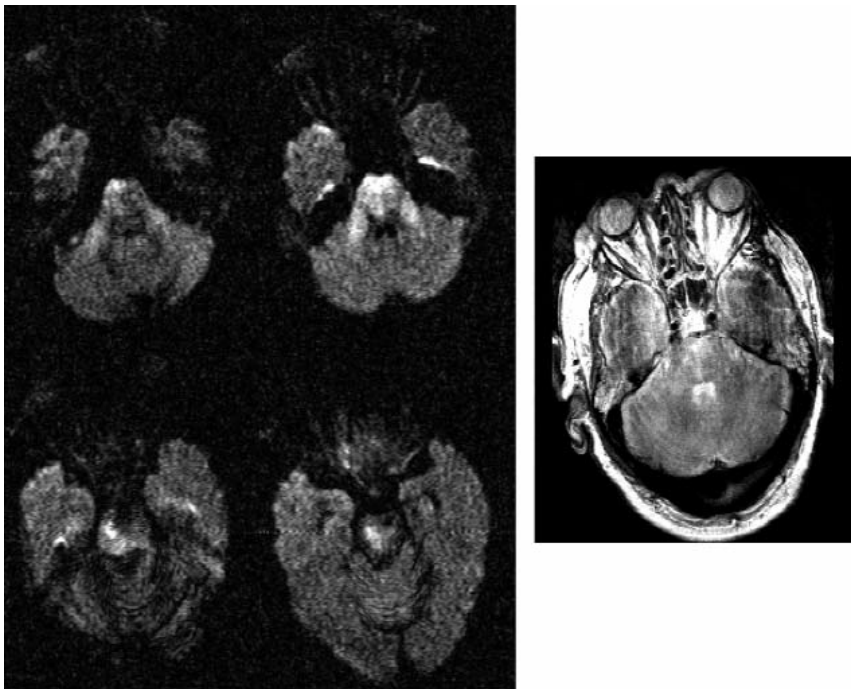

Figure 3. Same patient as in Figure 2, two weeks later, presenting tetra-paresis, reduced activity, dysphagia and anarthria, vagal stimulation during treatment causing bradycardia and coma due to a second, right acute pontine ischaemia demonstrated in a new MRI.

tentorial brain perfusion and cellular activity in both hemispheres. Thus a so-termed 'super-locked-in syndrome' might have occurred and only with additional demonstration of global loss of brain perfusion and absence of brain activity, the diagnosis of brain death might have been justified according to the rules in our country.

Brain Death Syndromes vs. Mimics: Clinical and Technical Issues

Clinico-pathological reports date back to the 19th century and many definitions of this syndrome have been proposed since 1876. In literature this syndrome is very well known, in Alexander Dumas' famous novel, *The Count of Monte Cristo*, where Monsieur Noirtrier de Villefort is referred to as the corpse with 'vivid eyes' and Emile Zola introduced the mother of

Camille Raquin, who communicated only with her eyes. In a more recent very nice book Jean-Dominique Dobe recounts the locked-in syndrome from a former patient's view, *The Diving Bell and the Butterfly*.

This syndrome is to be separated from other conditions such as vegetative state, where consciousness is lost. However, once the reticular formation and connections with the thalamus and cerebral hemispheres are destroyed and completely disrupted, the condition changes into what is termed the *brain stem death formulation* if persistent over time.

In the following I will concentrate on other specific brain-centred definitions of death and in particular work on both medically accepted definitions of death as *whole brain death* and *brain stem death formulations* versus the not medically accepted *neo-cortical formulation*. According to the neo-cortical definition of death, Terri Schiavo's case would have been considered death emphasising a fundamentally different concept: the irreversible loss of the capacity of consciousness and social interaction. Terri Schiavo was never brain dead but suffered from coma and vegetative state with intact or only moderately affected brain stem functions. The same is true for a patient who was nursed in our hospital for more than ten years after global hypoxia and persistent vegetative state.

Post mortem examination showed extremely severe atrophy of major parts of both hemispheres, thalamus and basal ganglia, both atrophic but macroscopically intact brain stem and cerebellum (Figure 4, see page 427).

Brain death formulations such as whole-brain death and brain stem death are medically accepted at least in different countries and have been successfully and beneficially used for decades, however, the *neo-cortical formulation* is not.

This most controversial concept of death originally supported by Scottish neurologists Brierley and his colleagues in 1971 urged that death be defined by the permanent cessation of 'those higher functions of the nervous system that demarcate man from the lower primates'. It has been developed further by others, mainly philosophers and its conceptual basis rests on the premise that cognition and social interaction, not the bodily physiologic integrity, are the essential characteristics of human life – thus if functions of the neo-cortex but not the whole brain, or brain stem are permanently lost, neo-cortical death results according to the promoters of this concept. However, neither clinical nor confirmatory tests have ever been validated, nor can they be established in a scientific way that would be reliably adjusted to an anatomical and functional criteria of present brain research. Today it is impossible – in contrast to brain death, for which

neuro-anatomy and neurophysiology are well-established – to determine human consciousness and *even less reliably* higher brain function by clinical or surrogate parameters, nor are there any *behavioural parameters* available showing that consciousness has been irreversibly lost. Patients in the vegetative state unlike patients with brain death, following an acute injury or chronic degenerative disease and anencephalic infants are considered dead according to this neo-cortical formulation, although they are often not apallic as previously thought and may show preserved islands of functional brain cortex. Neuroimaging studies – as nicely reviewed by Stephen Davis during this symposium – have shown re-activation in patients in a vegetative state and even recovery cortical functions after 19 years in a patient with minimally conscious state (MCS) as recently published (Voss *et al.*, 2006). These authors studied diffusion tensor imaging in two patients with traumatic brain injury (Figure 5, see page 428).

This technology allows demonstration and display of fibre connections in the brain, which are responsible for multi-focal and systemic network activity, underlying basically human brain function such as consciousness, recognition, attention, awareness, spontaneity, thinking, reflecting, communicating, memorising, suffering, laughing, creativity, intellect, etc.

Their patient, a 39-year-old male, who at age 19 suffered a severe closed head injury in a motor-vehicle accident, spontaneously emerged from MCS 19 years after the initial injury and recovered spoken language. He initially remained in a coma 1-2 weeks followed by further recovery to a vegetative state and subsequently a level of function existed of MCS within several months of injury. Although gradual improvements in responsiveness were noted over an ensuing 19-year period, the patient was unable to communicate using gesture or verbal output. Limited head nodding and grunting were only inconsistently present. Eight months prior to the authors' first evaluation, he spoke his first word after his brain injury ('mum'), which was followed by a recovery over a period of several days of increasingly fluent, but dysarthric speech and reliable communication. He was oriented to person but did not know his age, misidentified his location and indicated that he did not know the current year, selecting '1984', the year he was injured, from a list of four alternatives. Eighteen months later, at the time of the second diffusion tensor imaging scan, several areas of neurological improvement were identified: reassessment of motor functions demonstrated recovery of both lower extremities, which were paretic on initial examination, showed improvements in strength to at least 4 + / 5 on volitional movement. Cognitively there was an overall increase in baseline arousal combined by

generalised improvements in attention and focus and response persistence. He was able to count from 1 to 25 without interruption, speech intelligibility improved, he remained oriented to person only and conversational speech remained free of paraphasic and dysnomic errors. At the time of the first scan there were well-confined regions of pronounced right-left anisotropy in the medial, parietal and occipital (MPO) areas of the brain (visible as the red occipital areas in B). These areas were also significantly larger than in normal controls but reduced in the second scan 18 months later (E) and were no longer significantly separated from controls. However, another striking region of right-left anisotropy had become evident in the inferior part of the cerebellar vermis (H), directly correlating with the patient's regaining of limited use of the lower extremities motor function recovery as well as improvement of dysarthric speech disturbances.

Increased metabolic activity in the MPO regions in a PET-CT scan was consistent with these findings.

In summary, the authors have taken the initiative to carefully check this individual's history and personally examined this 'miracle recovery from coma', which was widely discussed in the popular media. The MRI assessment of transiently increased fractional anisotropy and directionality in the posterior midline cortices, interpreted as increased myelinated fibre density and novel cortico-cortical sprouting paralleling the emergence of the patient from MCS is a most remarkable and unique finding in the literature. As this patient's brain also showed amplified metabolic activity measured by PET these structures seem to be of importance in consciousness of self and interaction with the environment and hence for future research a most challenging area: this is further supported by previous knowledge that this area is very active in conscious waking and in altered states of consciousness, such as pharmacological coma, sleep, dementia and post- and anoxic amnesia. It has been assumed that it is originally connected multimodal associate area in the neuron network subserving human awareness. However, this patient like others in less spectacular cases was *not considered brain dead in the term of whole brain death and brain stem death formulations* but was consistent with the concept of death in the neo-cortical formulation. This underlines the importance of a strict separation and differentiation of patients with chronic unconsciousness, or minimally conscious patients, where even painful stimuli do not elicit any cortical activity as seen on functional MRI scans.

To summarise, brain and brain stem death, vegetative state and locked-in syndrome are different entities, clinically as well as during technical

studies: if adequately and accurately diagnosed they can be separated, as well as consciousness and sleep versus anaesthesia can be separated, or the vegetative state and the minimally conscious state in chronic patients with severe brain lesions. Severe destruction of parts of the brain is more than the sum of its parts and may be consistent with brain death according to clinical and biomedical testing, however, survival of parts of the brain are also more than parts and may be consistent with a living brain.

More recently fMRI studies and PET testing became available as research tools and in addition to new molecular biological tests, these techniques may provide useful information to a better understanding and knowledge about this complex issue and the underlying physical and metaphysical changes in the process of dying, which to some extent and purpose are well known and useful in clinical medicine, however, to some extent they are still poorly understood and insufficiently termed.

New vs. Old Concepts and Definitions

At present the best accepted definition of death is the 'permanent cessation of the critical functions of the organisms as a whole' (Bernat, 1998). This traditional concept refers to functional integrity – not simply representing some of its parts but of course including important critical functions, such as control of respiration and circulation, neuroendocrine and homeostatic regulation without which the organism cannot work and hence they are all irreversibly lost. However, this concept also implies that when cardiac function ceases, the patient is dead: this rationale has *regained* interest once the discipline of transplantation surgery has matured and the number of patients with end-organ failure eligible for organ replacement surgery has increased. Despite the growing demand 'for organs' the number of potential 'brain-dead donors' remains limited and hence, a new group was declared dead by cardiopulmonary criteria: the *non-heart beating donors* (NHBD).

Essentially this group was already the major source of organs for transplantation prior to development and adaptation of brain death criteria and remained so in countries such as Japan, where the concept of brain death has only recently been a subject in legislation, but not widely accepted by the general population. Furthermore, the determination of death by cardiopulmonary criteria is by far better accepted in the general populations around the world and the pool of potential donors would include a larger group of patients, not only those patients dying from catastrophic brain injury. However, there are major ethical concerns with the use of NHBD, in

particular as questions about time, timing and the determination of death are crucial: e.g. is there a specified duration of absent cardiac activity and how long is it? Is this period not associated with spontaneous 'auto-resuscitation' and hence in the absence of activity should be considered reversible? Are 2-20 minutes of asystole reasonable estimates of this period and are they sufficient to avoid organ damage due to 'warm ischemia'? And, if it requires ten or more minutes without perfusion for the brain to die, how can its status be ignored after a shorter time? This raises the issue of a patient experiencing pain or worse, regaining consciousness when cardiopulmonary function and brain perfusion are restored by mechanical means, such as intermediate cardiopulmonary by-pass.

The term 'brain death' has become so familiar that it is not likely to be replaced by a more precise and less confusing term, as proposed in an editorial in *The New England Journal of Medicine*, e.g. 'brain-based determination of death'. Furthermore, death is as reflected by the issue of the concept of non-heart-beating donors, a complex issue itself not only from a biological and medical point of view but also from a philosophical and ethical point of view. With terms such as brain death used by doctors, it is difficult for families to understand on the basis of a diagnosis of death, when the respirator-supported body of their loved ones manifests many signs of life. Many decades after its introduction this term still causes confusion among the public and healthcare personnel alike. Despite good and sufficient reasons why the existing consensus about the determination of death has endured more than thirty years in the face of persistent criticism, reconsideration of terminology along new details of investigation of the biological transition from life to eternity or whatever people expect and believe after this final period, remains a matter and challenge for modern medicine. Whether or not a recent proposal (Zamparetti *et al*., 2004) reverting the old term of 'irreversible coma' to 'irreversible apnoeic coma' is helpful and acceptable has to be seen. Such a term could abandon the presumption of diagnosing the death of all intracranial neurons and/or the patient's biological death.

Whether or not death is a process or an event can be discussed ad infinitum, remembering the longstanding growth of hairs, nails, skin and bone cells, days and months after death. Rather death may be regarded as an event that separates the continuous process of dying, from subsequent disintegration, which arrives at a certain borderline where irreversibility is reached and a point of no return can be identified. Traditionally, and prior to the invention of artificial mechanical ventilation in intensive care units, a circulatory relation of death was defined by the irreversible cessation of

circulation in this process: whether at home or in the hospitals, most of the people 'died and still die their own deaths', without machines or elaborate interventions being involved. The irreversible loss of the capacity to breathe spontaneously and hence to maintain a spontaneous heartbeat, thus defining death of the whole organism in traditional form. Both are essentially brain stem functions and both can be taken over by machines before a certain period until recovery of brain stem function or in the presence of functional integrity of the brain stem. However, if catastrophic brain stem lesions cause irreversible destruction of both critical brain stem capacities, life can no longer persist without mechanical support, exactly a situation that is described by 'permanent loss of the breath of life' and forms the implicit basis of the UK formulation in diagnosing brain stem death.

The whole brain formulation requires the bedside demonstration of irreversible cessation of all clinical functions of the brain and is the most widely accepted. The brain stem formulation regards irreversible cessation of clinical functions of the brain as not only necessary but also sufficient for the termination of the death. Brain death is classically caused by a brain lesion, resulting in an intracranial pressure higher than the mean arterial blood pressure. This causes intracranial circulation to cease and brain stem damage to herniation. However, the brain stem formulation of death may be applied to cases of catastrophic brain stem lesions (often of hemorrhagic original) that spared the thalami and cerebral cortex and even leave intracranial circulation intact, which would be sufficient according to the brain stem formulation, even in the absence of raised intracranial pressure. Theoretically multiple brain stem lesions could selectively impair all brain stem function that can clinically be tested, while preserving residual (but clinically undetectable function) of the reticular activating system – in practice no such cases have ever been reported, if confirmatory examinations by two independent physicians experienced in intensive care unit medicine and neurology are requested. With repeat testing after strictly defined intervals and surrogate studies according to meticulously defined protocols and legal regulations are sufficient and widely used safe requisites.

Some people have criticised the brain-centre definition and advocated circulatory formulation of death only as we all know. In this view a living body possesses not only integrator but integration, a holistic property that derives from interaction among all parts. However, functions of circulation, respiration, homeostasis and neuroendocrine regulation are all regarded as critical functions, which, if irreversibly and permanently lost are inevitably followed by cardiac arrest: (no single case has been reported since their use

in 1959, where appropriate history taking diagnosis of circumstances and conditions and appropriate testing by experienced physicians were unreliable and caused misdiagnosis) hence the neurocentric criteria of death may be considered among the safest medicine which can be achieved.

Conclusions

In conclusion: i) brain death is death, but an irreversible vegetative state is not; ii) the whole brain and brain stem formulations determine both death; iii) irreversible cessation of critical functions of the organism, which means neuroendocrine and haemostatic regulation, control of circulation and respiration as a whole are accepted and practiced criteria worldwide; iv) 'the whole brain formulation does not require confirmatory tests for brain death' but 'the brain stem formulation may'. Future technology might be useful to support this concept further. Julia Chan recently reviewed a framework of transnational research on brain stem death, that is based on systematically coordinated, clinical and laboratory efforts centred on this phenomenon. It begins with the identification of novel clinical markers from patients suggested to be related specifically to brain stem death. The author has voted the idea that 'life-and-death-signals' are related to functional integrity of the brain stem, expressing traces to the rostral and ventro-lateral medulla and having been applied to animal models of brain stem death to provide a notion of both 'pro-life' and 'pro-death' programmes, actively involved in the progression towards death. These programmes involve mitochondrial functions, nitric oxide, peroxinitrate, superoxide aneon, coenzyme QT, e-shock proteins and ubiquitin-proteases. The authors propose that such programmes are involved in the neurosubstrate determining the final fate of the individual (being dead by definition). Parameters such as these are suggested by the authors to identify regulatory mechanisms becoming active at the life-death border and hence challenging our scientific knowledge about many questions in this crucial area which still remain open.

Whether or not future technologies may one day change our current ideas of irreversibility and cause revision of the definition of death remains to be seen.

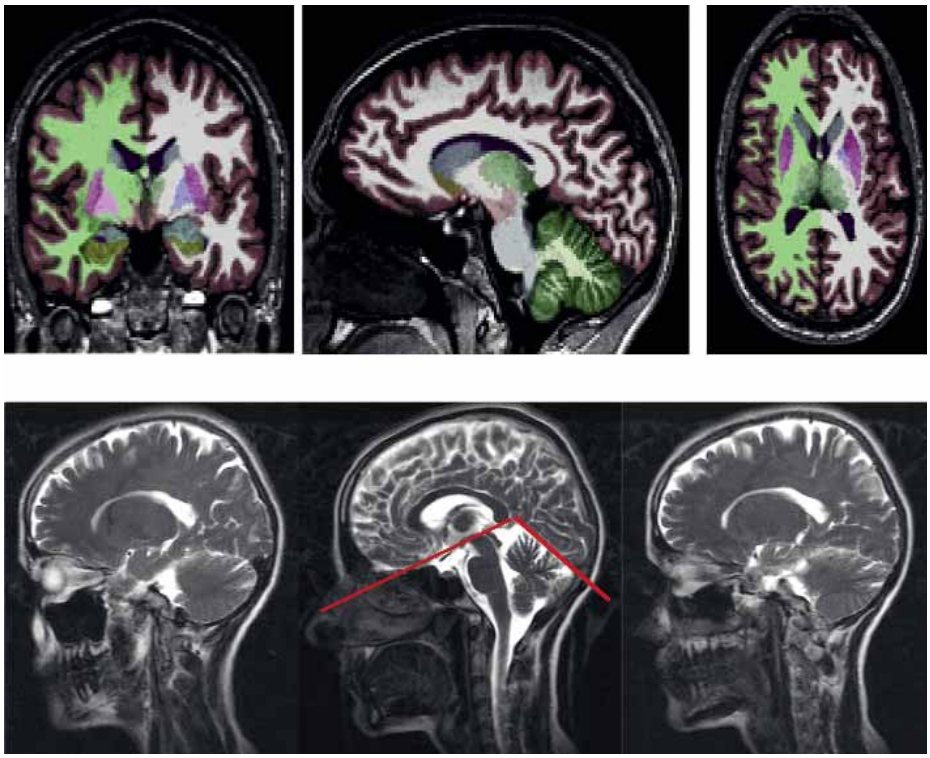

Figure 1. Sagittal, lateral and horizontal projections of the human brain in the MRI scan. Red lines separate cerebellum and brain stem from supratentorial structures.

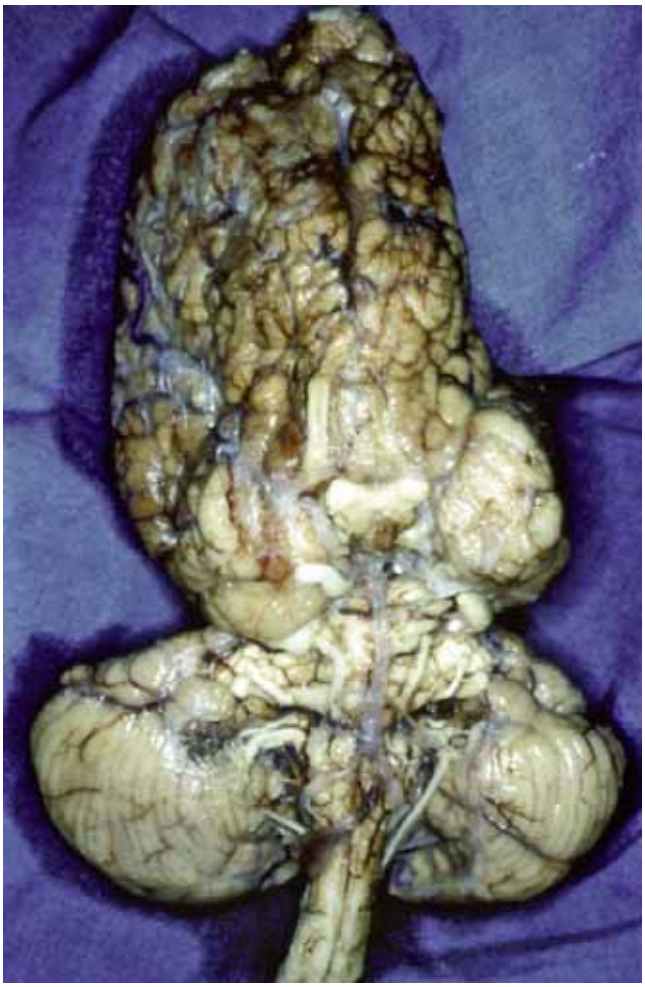

Figure 4. Post-mortem brain of a patient who suffered a vegetative state for more than 12 years – severe destruction of the supratentorial brain structures with preservation of pontine and cerebellar segments.

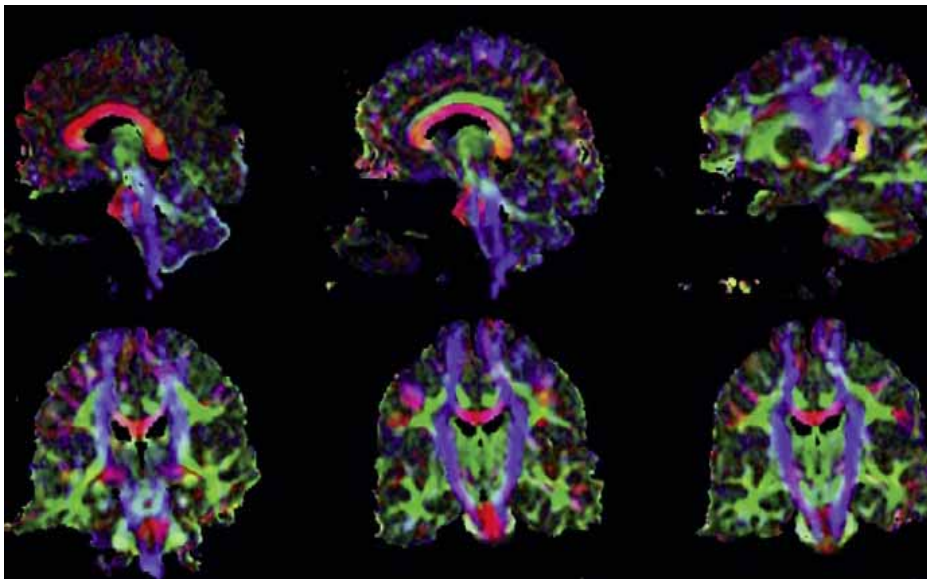

Figure 5. MR Tensor images of white matter pathways in a human brain (*red* indicates horizontal, *green* anterior-posterior and *blue* proximal-distal fibre connections).