

NEUROLOGICAL DETERMINATION OF DEATH IN ITALY

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Keywords - Brain death, determination of death, dead donor rule, intensive care

Summary - Forty years since its definition by the Ad Hoc Committee of Harvard Medical School in 1968, the neurological standard for determination of death maintains all its validity and acceptability. The biological and philosophical rationale underpinning the irreversible loss of brain function proves its equivalence with the death of an individual, even when circulatory function is prolonged. Although the neurological standard of death has not changed in the past forty years of application in hundreds of thousands of deaths in almost every country in the world, it has yielded an enormous wealth of clinical and instrumental experience.

In Italy the 1993 law enshrined the clear-cut separation required between the determination of death and the possibility of organ donation. Following Decrees and guidelines require detailed clinical and legal procedures approved by several specialists, and offer an abundant guarantee of completeness, accuracy and certainty in the declaration of death by both cardiac and neurological criteria.

The determination of death by neurological criteria is currently a consolidated practice in Italian intensive care units (around 2200/year) flanked by a major fall in mortality rates for patients with acute brain lesion. This has a strong ethical, moral, but also purely clinical value and is a consolidated asset for Italian doctors, understood and widely shared by the population who are constantly given accurate and appropriate information.

In this paper scientific, philosophical, ethical and moral critical points are discussed in the light of the accumulated evidence of consolidated medical practice, in relation to the Italian medical and social context.

Despite differences of opinion and doubts reported in the press and medical literature over the years, the neurological diagnosis of death has in the vast majority of cases ensured the utmost respect for the dignity of death for patients and their relatives in the secure knowledge that there is no possible chance of recovery. At the same time in some cases it has allowed the donation of organs as one of the finest gestures for the benefit of humankind.

Introduction

Despite treatment with the most advanced intensive care and neurosurgical techniques currently available, a small percentage of patients with acute brain lesion (due

to trauma, stroke, infection, anoxia, cancer) will die. Thanks also to intensive care and diagnostic and surgical advances, the mortality rate of these patients has declined substantially since the 1960s when many patients with devastating brain injury were resuscitated and kept alive on life-support systems. These patients had lost not only consciousness but also all brain stem reflexes, spontaneous breathing and cortical electrical activity. They were described and defined as being in a “*coma dépassé*” by French neurologists Mollaret and Goulon in 1959. All of these patients would invariably die at some point from

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cardiocirculatory arrest and all presented colliquative brain necrosis.

The neurological standard of brain death defined by the Harvard ad hoc committee in 1968 stemmed from the many clinical, pathological and instrumental (namely electroencephalographic) observations available at the time. Beyond a doubt transplant medicine in those years served to stimulate a definition of the neurological criteria of death. The initial overlap also in legislation between the removal of organs and the diagnosis and declaration of “brain” death in Italy with the 1975 law raised doubts that such diagnosis was an ulterior purpose designed to serve transplantology and not an adequate biological, scientific, philosophical, moral and legal concept.

Paradoxically, advances in cardiopulmonary resuscitation techniques and extracorporeal support of cardiocirculatory function did not raise similar doubts over the diagnosis of death by cardiocirculatory criteria despite many case reports of apparent death, mainly linked to hypothermia. Although the unitary mechanism of death in case of acute brain injury and cardiocirculatory arrest is massive cerebral infarction with irreversible loss of brain function, determination of death from cardiocirculatory arrest is confined to the absence of electrocardiographic activity for a few minutes and is seldom carried out in daily clinical practice. In the vast majority of cases death is still declared after at least 24 hours observation of the body in the mortuary. The possibility of removing organs from non-heart-beating donors currently poses once again the complex critical aspects of diagnosing death by cardiocirculatory criteria with respect to the need to minimize the warm ischaemia time for each organ. Despite the importance of this topic it is not among the aims of this document.

Although the neurological standard of death has not changed in the past forty years of application in hundreds of thousands of deaths in almost every country in the world, it has yielded an enormous wealth of clinical and instrumental experience. The accumulated evidence of consolidated medical practice now allows a documented scientific, philosophical, ethical and moral reassessment of the topic of brain death.

Despite differences of opinion and doubts reported in the press and medical literature over the years, the neurological diagnosis of death in the past forty years has in the vast majority of cases ensured the utmost respect for the dignity of death for patients and their relatives in the secure knowledge that there is no possible chance of recovery. At the same time in some cases it has allowed the donation of organs as a great act for the benefit of humankind.

The neurological determination of death is legally recognized as the death of the individual in the vast majority of countries in the world (Wijdicks, 2002; Haupt and Rudolf,

1999). Procedural differences and peculiar objections (Japan, New Jersey) reflect different cultures, religions and medico-legal and forensic traditions but do not affect the core criteria defined by the Harvard committee in 1968.

Italian citizens enjoy highly protective legislation. The latest law 578/93 defines death as an irreversible loss of all brain function and Decree 582/94, reviewed in 2008, with the attached scientific guidelines, provides the procedures for the determination and declaration of death by extremely cautious neurological or cardiac criteria, taking into account the technological advances in medicine with abundant clinical, instrumental and medico-legal procedural guarantees. It should be emphasized that the 1993 law is quite separate from the activities of removal and transplantation of organs. Declaration of death is compulsory in any case identified and irrespective of the possibility of removing the patient’s organs.

Aims

The aim of this paper is to respect the indispensable synthesis between the two key aspects of medicine based on scientific acquisitions weighed against ethical, moral and philosophical issues, but also substantially forced into a contemporary debate in the setting of shared medical practice.

For this reason it is useful and important to analyse some of the aspects characterizing the discussion of brain death in the first forty years of applying the neurological standard of death, also in the light of the recent debate on end-of-life issues in Italy and the recent document (December 2008) produced by the Council on Bioethics set up by the previous President of the United States and specifically entitled “*Controversies in the Determination of Death*”. The main question to which this document gives a confirmatory, albeit not unanimous, answer is: “*Is the neurological determination of death the death of the human being?*”.

Problems linked to the terminology, definition and concept of death

A certainty of exceptional moral weight and two main criticisms have emerged with respect to the rationale underlying the neurological standard of death long exemplified by 1) the irreversible loss of all brain function due to death of the whole brain, including the brain stem; 2) the irreversible loss of the supreme organ and its irreplaceable and indispensable function as the body’s controlling organ as the *sine qua non* of living beings and the possibility to maintain cardiocirculatory function:

1. Residual brain function is evident in some patients meeting the neurological standard for determination of death.

2. A minimum level of biological *integration* remains and is sufficient for prolonged maintenance of extracerebral functions, namely cardiocirculatory function, if intensive care and mechanical ventilation is ensured.

3. No recovery of the brain function on which the neurological standard is based has ever occurred in any patient.

Point one: the fact that the moment of cessation of all brain function corresponds to whole brain death is not entirely true. Isolated areas of brain activity, mainly assessable solely with instrumental tests but well-documented, can coexist alongside the loss of all explorable brain function. In addition, *diabetes insipidus*, resulting from necrosis in the hypothalamic nuclei and posterior hypophysis, may be absent. This may be related to a partial physiological irroration of such nuclei by the extracranial circulation.

Nonetheless, any persistence of residual metabolically active cells within the brain does not invalidate the concept of death of the individual. The United Kingdom has adopted a definition of death that includes the *irreversible loss of consciousness and breathing*. For this to occur from a pathophysiological standpoint, necrosis of the *brain stem* is required. The brain stem houses 1) the activating reticular system (projecting to the thalamus and cortex) responsible for arousal and wakefulness and hence awareness; 2) the cluster of cells responsible for the fundamental and intrinsic drive of spontaneous breathing; 3) the descending motor and ascending sensory pathways that transmit impulses to the rest of the body and process information from the external environment determining even a minimal possibility of relation; 4) the nuclei and afferent and efferent pathways of the cranial nerves whose clinical examination alone together with the apnoea test will allow an accurate, rigorous and certain determination of the complete loss of function throughout the brain stem. Clinical examination accompanied by the established pathogenesis and severity of brain injury will define the total necrosis of the brain stem and is the crux of the neurological standard of brain that has remained unchanged from the 1960s to date.

The same examination will distinguish any other clinical situation beyond doubt, namely "*vegetative state and minimally consciousness state*" often associated or even confused or deemed similar to "brain" death. In fact, the basic difference between the two lies in maintenance of brain stem function, albeit impaired, i.e. the wakefulness capacity, the essential prerequisite of consciousness and spontaneous breathing. Coma is a transient situation abolishing the state of wakefulness and consciousness with preserved spontaneous breathing and at least partial brain stem function. With treatment coma will evolve into a recovery of the state of *wakefulness* in most cases, whereas in some patients the state of wakefulness will be recovered but not that of consciousness ("*vegetative*" state), or

coma will evolve into a *minimally conscious state* difficult to discern. The complete irreversible loss of the capacity for consciousness and spontaneous breathing is associated with total necrosis of the brain stem and can be diagnosed by the Harvard neurological standard. This will allow and exact, completely reliable and accurate differentiation of any other clinical situation of "*brain failure*", even the most severe and compromised, that does not constitute *total irreversible brain failure*.

A systematic examination of all brain stem reflexes is intrinsically "redundant", but only a full clinical examination and the apnoea test using strict standardized criteria offer an extreme guarantee ruling out borderline situations of "almost total" brain stem injury with partial preservation mainly of the *medulla oblongata (bulb)* responsible for spontaneous breathing ("*medulla man*") (Wijdicks *et al.*, 2001). In particular, given the peculiar anatomical and pathophysiological features of the newborn brain and cranium, total necrosis of the brain stem and brain must be proved with extreme rigour and confirmed by the absence of flow test. Some of the newborns and children described as cases of "*chronic brain death*" by Alan Shewmon (1998) could have arisen from incomplete necrosis of the brain stem bulb (Wijdicks and Bernat, 1999). In this setting, Italian legislation has enshrined strict rules for diagnostic certainty.

In almost all Countries the concept of whole brain death has prevailed over that of brain stem death in the scientific and legal implementation of the standard for neurological determination of death (Bernat, 2006). Paradoxically, this has given rise to the criticisms reported above on the possibility of residual areas of brain function that constitute a semantic, if not substantial, contradiction to the concept of *whole brain necrosis*. In the determination of "*whole brain death*" confirmatory tests following clinical diagnosis may occasionally disclose cortical electrical activity, albeit residual and temporary, and minimum irroration of the cerebral vessels (especially when direct injury is confined to the brain stem) thereby excluding the determination of death in these patients. On the other hand, detailed and sophisticated imaging techniques demonstrating beyond doubt the total absence of cerebral blood flow are the best means of depicting in both pathophysiology and communication the simple concept of "*decapitation*" of the individual as the basis for the determination of brain death. Moreover, the criteria adopted to determine absent cerebral blood flow do not address the real effective perfusion of the cerebral parenchyma but offer a simple and clear-cut demonstration of total interruption of flow at the entry to the cranium both for the anterior carotid circulation and the posterior circulation supplied by the vertebral arteries. This offers an absolute guarantee of absent flow within the cranium and

hence no possibility of cerebral function or metabolism, well beyond the quantitative determination of the real needs of perfusion to maintain the vital functions of the cerebral parenchyma.

Point two: The brain is not a single system integrating the whole body in an all-or-nothing fashion. The biological concept of death as the irreversible loss of the integration of the organism as a whole underlies the legal implementation of the equivalence between the neurological standard produced by the Harvard committee in 1981 and the death of a human being, proposing the *Uniform Determination of Death Act* in the same year. This axiom was based on the clinical and pathophysiological situation in the setting of the technical possibilities of intensive care medicine of the time and the evidence that all individuals with brain stem necrosis soon suffered circulatory arrest as a direct consequence of the loss of brain control over all bodily functions. The concept of death as an irreversible loss of all capacity of coordinating and integrating physical and mental functions was adopted by the Pontifical Academy in 1985 and by Pope John Paul II in 2000.

In practice, literature reports, mainly papers by Shewmon, and current clinical experience demonstrate that intensive care medicine techniques can compensate the loss of brain function for months on end with ventilatory and circulatory support. Apart from the isolated observational studies on patients with loss of all brain function treated *ad libitum*, these techniques have been employed in pregnant women to allow adequate foetal maturity prior to delivery. In these cases, prolonged intensive care maintained a physiological uterine environment within the body of a pregnant woman when death was not declared even if the neurological standard of death was present, but was artificially postponed until after delivery. Pregnancy could not have continued in Italy once death had been declared so a “legal stratagem” was devised, with the approval of the ethical committee and the patient’s relatives, for the primary good of the foetus.

Therefore the brain is not an organ totally and solely responsible for integrating all other organs and functions and without which the body will rapidly disintegrate. In practice, central nervous system function below the occipital foramen (*spinal cord*) is maintained by a much more modest but objective capacity for functional integration. This function is normally regulated and *modulated* by the brain, using a *negative feedback mechanism* to respond to any possible internal or external change in the body’s homeostasis. After a “*spinal shock*” primitive medullary diastaltic reflexes help to re-establish a minimum level of circulatory integration, viscerovisceral and motor reactions (*spinal reflexes*) and metabolism under poikilothermic conditions (loss of strict regulation of body temperature in the physiological range). This is accom-

panied by functions that are not strictly brain-dependent such as the immune response and the inflammatory and biohumoral responses, etc. Such basic functions, provided by artificial life support to maintain breathing and hence circulation, can be deemed conceptually similar to some functions evident in the period following death due to cardiocirculatory arrest that continue because they do not require the maintenance of blood irrigation (growth of nails and hair, etc.).

The severe cardiocirculatory instability frequently accompanying the passage from coma to death is largely determined by the consequences of the *autonomic storm preceding* necrosis of the bulb (the extreme consequence of severely ischaemic but still vital neurons in the medulla oblongata) and mediated by an enormous *adrenergic discharge* (sympathetic-adrenal system). This may result in pulmonary oedema, coagulation changes and severely impaired cardiac contractile efficiency, favouring shock and early cardiocirculatory arrest when adrenergic tone rapidly declines due to bulbar necrosis.

A prospective study designed to establish the limits and types of intensive care support for an individual presenting the neurological criteria for determination of death is not feasible for ethical, moral, legal and social reasons, but this in no way changes the concept of irreversibility and death.

Point three: A simple truth emerges from the literature and the clinical experience of hundreds of thousands of cases in the first forty years of application of the Harvard standard: despite any possible minimal residual intracranial activity and persistent integration sufficient to allow prolonged resuscitation with ventilatory and circulatory support, no recovery of cerebral function is possible and hence the damage is irreversible. This evidence offers a great deal of moral support to the neurological standard for the determination of death.

To contradict the concept of death and its legal value on the basis of an incomplete validity of the total loss of the single organ integrating the body, a concept backed by massive evidence that no recovery of brain function is currently possible in modern medicine, would force intensive care physicians to take a journey back through time. This would mean maintaining such patients on life support systems until circulatory arrest or therapeutic desistence and “ethically justifiable” suspension of ventilation, in the absence of specific legislation or universally shared procedures on “*end-of-life*”. It would be like reaching the paradox of indicating immediate hibernation for all individuals in cardiocirculatory arrest, to prevent disintegration of the body, awaiting hoped for future advances in medical technology allowing regeneration, repair or substitution unimaginable at present. But combating the body’s disintegration process when brain function is irreversibly lost precludes any clinical recovery.

Why is the standard for the neurological determination of death valid?

Acceptance of the neurological concept of death must be based not only on a moral principle but above all on a philosophically acceptable biological situation.

Is there a rationale by which the irreversible loss of whole brain function, essentially based on the substrate of brain stem necrosis (with irreversible loss of the capacity for wakefulness and hence the capacity for consciousness and the capacity for spontaneous breathing), constitutes the biological, philosophical and hence also legal death of a *individual*, in the sense of a *living being in his/her entirety*?

Firstly, the *concept* of death must be kept separate from the *criteria* for its determination. If death is basically a biological event, the concept of death of an individual must be unitary and cannot be confused with the death of cells or individual body systems. Death must be an immutable, definitive, obligate, independent point at which a person ceases to be alive. The criteria for the determination of death must possess a high degree of accuracy, reproducibility and sensitivity to rule out false positives with certainty, i.e. to eliminate any likelihood of determining the death of a being still alive.

With its meticulous observation of the clinical prerequisites, methodology, procedures and possible recourse to confirmatory tests, the Harvard neurological standard constitutes the internationally recognized and applied core of the determination of death and offers abundant certainty of avoiding error.

In the presence of doubtful residual cerebral function (no evident poikilothermia, diabetes insipidus and a tendency towards hypotension) that per se does not contradict or invalidate the neurological standard, it could be useful in any case to perform the flow test to gain the utmost evidence and guarantee of *total irreversible brain failure* (Verlato, personal communication, 2005).

The neurological standard, including the certainty of the etiology of the brain lesion, will distinguish total brain stem necrosis from any clinical situation other than death, even the most subtle imitation of certain clinical signs (*locked-in syndrome, brain stem encephalitis, Guillain Barré, intoxications, etc.*). The Harvard clinical standard, confirmed when necessary by instrumental tests readily available nowadays in intensive care units, has the maximum sensitivity and specificity in identifying with certainty the neurological criteria for the determination of death.

But why accept that the brain as a single critical system whose irreversible destruction is the condition both necessary and sufficient for the determination of a person's death?

Is there a pathophysiological rationale for the neurological standard of death?

Conceptually speaking, death can be considered an event permanently ending a person's life separating the dying process leading to death from disintegration of the body, a process that occurs after death. During the dying process resuscitation, for example, can revive a patient in cardiac arrest until circulatory arrest causes death from permanent total brain infarct. This is the point of no return, the moment of death that terminates the dying process. We know that sometimes inappropriate resuscitation attempts can lead to restoration of cardiac activity and blood flow when the point of no return is long past. In this case the person's death must be determined by neurological criteria. At other times cardiac activity is restored in an intermediate period in which the brain stem is more resistant to anoxia-ischaemia than the cortex and this will probably entail survival in a "vegetative state". To determine death using cardiac criteria a complete absence of heart beat and circulation must be observed for at least the time required for brain necrosis to occur with certainty so as to determine the irreversible loss of all brain function. Likewise, in the process of dying caused by acute brain injury and by progressive brain ischaemia when the patient is on life support neuro-intensive care and neurosurgical treatment may lead to resuscitation until the point of no return is reached. Some authors (Zamperetti *et al.*, 2004) have criticized the definition and terminology of "brain death" suggesting it be replaced by "*irreversible apnoeic coma*". In practice they identify this situation as an extremely advanced point of no return such as to fully justify the suspension of ventilation and circulatory support and also organ removal. The Danish Council of Ethics also developed a perspective allowing the removal of organs without having first legally determined a person's death as this would bring an end to the dying process but would not be the cause of death cause.

In practice it seems logical and sustainable that in both dying processes, neurological and cardiac, the point of no return should identify not cardiac or brain death but the death of an individual.

Is strict observance of the neurological determination of death and of the "dead donor rule" still necessary?

The neurological determination of death is based on biological and philosophical criteria that have been criticized by some authors, some of whom are physicians (Shewmon, 2001). If the legal recognition of death thus determined were abolished, a dramatic dilemma would arise in re-

suscitation as it did in the 1960s, paradoxically exacerbated by the enhanced capacity for prolonged circulatory maintenance. Individuals for whom death could not be determined would be treated differently depending on the presence and validity of specific declared intent, the legal acceptance of systematic therapeutic desistance in patients with no possibility of recovery, giving rise to situations of conflict, uncertainty and anxiety amongst intensive care physicians and patients' relatives. In Italy this would likely generate ongoing legal, political and social conflict.

This could also lead to a loss of the "dead donor rule" that has been the ethical, moral and social principle shared by physicians and the population alike since the 1960s and the start of transplant medicine. A headlong rush towards removing organs from "dying" individuals without the legal determination of death on the basis of advance informed consent, as initially proposed by Troug and Robinson (2003) and subsequently repropounded by Zamperetti *et al.* (2004), could give rise to a dramatic situation of uncertain complexity and conflict, especially in Italy. Such a stand would make it even more critical and difficult to use individual freedoms expressed as advance intent and informed consent, when they could give rise to a variable and subjective determination of the time of one's own death from cardiocirculatory arrest caused by organ removal. For those that fear and stigmatize the proximity of the neurological determination of death as an ulterior motive devised to favour organ removal, abolition of the "dead donor rule" would have the paradoxical outcome of abolishing the fundamental point guaranteeing that the biological and legal entity of death is the irrevocable requirement for organ donation to be accepted and proposed by all social, medical and religious institutions as a moral act and one of the finest gestures of solidarity and charity towards others in need. Such a gesture cannot legally and morally entail the active suppression of a patient, even with his/her consent, to the advantage of others. Awareness of the certainty of death as the requirement for donation is currently the most critical point in advance consent, either in favour or against, for most Italian citizens, especially in talking with family members in the intensive care unit.

The "dead donor rule" is the key point for a person irrespective of the possibility of organ donation. Brain death is an unnatural situation created by the possibility of artificial ventilation in individuals with such extensive irreversible brain injury as to cause total brain destruction. If death were linked to cardiocirculatory arrest these individuals could paradoxically "remain eternal" because they would be kept on mechanical ventilation and artificial life support indefinitely. In practice, cerebral destruction has already caused death that will also result in cardiocirculatory arrest once ventilatory support is withdrawn.

Nonetheless, the point of no return needs to be defined as it is mandatory that each individual be ensured the "right" of temporal recognition of death. This is why the moment of death must be defined.

Is there a biological and philosophical rationale for the neurological standard of death?

There cannot be different concepts of death based on different criteria to consider an individual no longer a living human being. In particular, the criterion proposed by some authors, linked exclusively to the *irreversible loss of consciousness* is unacceptable and dangerous both because consciousness is quantitatively and qualitatively difficult to gauge and above all because such a criterion would readily lend itself to possible discrimination and ethical and legal relativism.

There must be a unitary vision making a clear-cut distinction between life and death. The *Council on Bioethics*, set up by President Bush, carefully reassessed the concept of the death of an individual, no longer sustainable as the loss of the indispensable organ (the body's integrator) without which circulatory arrest and disintegration of all body systems can only be postponed for hours or days.

At first sight, the loss of spontaneous breathing is a loss readily compensated nowadays by artificial support and common to myriad acute and chronic diseases that are irreversible but nothing like death. In practice, the total and irreversible loss of brain function, namely the capacity for consciousness and spontaneous breathing, eliminates *irreversibly and permanently the possibility, capacity and intrinsic stimulus, the drive* living organisms must have to maintain their integrity and vitality. This can only occur through *aperture* and *interaction* with the environment by means of the intrinsic stimulus for vital maintenance *in primis* by the respiratory stimulus. This *fundamental vital work* is the intrinsic hallmark of living beings that is permanently lost at the moment of death.

This convincing, well understandable and sufficiently specific rationale is based on three points:

1. No part of the brain is absolutely indispensable for cardiac muscle contraction that has its own intrinsic rhythmicity and its contractility can be preserved even outside the body by artificial perfusion and oxygenation. Cardiac function per se cannot represent the body's vitality in its "entirety";
2. Current resuscitation techniques could probably postpone circulatory arrest *ad libitum* even though a prospective study on this topic would not be acceptable;
3. By contrast, the irreversible loss of the "neural driving force of existence", as an essential vital function exclusive

to the brain seems to be the indispensable and sufficient rationale for determination of death of a human being. Man's mental biological and ontological characteristics preclude assimilating life at birth to life nearing its end. Hence it is clear that the criteria defining death belong to the "no longer" category and cannot be transferred to life at birth where the categories "already" and "not yet" apply. It is now plain that much of the bioethical debate developing is strongly conditioned by this confusion, and by the fear that different schools of thought take advantage of apparent analogies to broaden or restrict defining criteria from the beginning to the end of life or vice versa.

In this sense it should be emphasized that:

1. The scientific community directly dealing with brain death and concerned with its study for half a century univocally deems the neurological standard of death to be valid and currently applicable; "[...] brain death is the bioethical issue on which the most consensus has developed in the recent history of medicine" (Bernat, 2008), and despite some criticism the "Harvard criteria" are currently enshrined by the scientific societies and legislation of almost all countries.
2. When the scientific community tackles the problem of defining death, it does not claim to substantiate it from all standpoints be they ontological, philosophical, spiritual or anthropological. The scientific community refers to death solely to distinguish a corpse from a person, to be able to give persons treatment and corpses due burial. It always uses the term "human death" or "death of a person" from a retrospective viewpoint, i.e. to claim that death has occurred with certainty and that we are dealing with a corpse.
3. Much attention should be paid to avoid confusing just definitions with debatable aims, and this must occur in both senses. On the one hand, attention focused on the brain to identify the cadaveric state cannot nor does it intend to herald the use of neurological categories to identify a person at birth or to resolve any other bioethical controversy. On the other hand, concerns over these other issues cannot bring us to deny the evidence that a brain that has irreversibly lost all its functions will identify a corpse beyond doubt.

Only an intellectually transparent reading of events observed scientifically for more than half a century can quell a debate aroused not by the doubt that a corpse is such here and now, but by the feared or hoped for consequences of inappropriate shifts of concepts from the end of life to its start and vice versa. For many decades technical opinion has been unanimous, with sporadic challenges to brain death published here and there and regularly disproved by a consolidated and widely shared teaching. Only when attempts were made to force the very concepts of something beyond the end of life to apply them by analogy to other

bioethical issues did the debate assume some relevance, albeit outside the accredited scientific community actually involved in declaring brain death.

This made it urgent to stress that:

1. The "dead donor rule" and the rules for the determination of brain death offer a guarantee for any other form of life, however maimed and weak it may be or appear to be, as no disease and no human condition can be included in the criteria defining brain death (not even anencephaly);
2. The criteria for the determination of brain death cannot in any way be transferred to bioethical issues concerning the beginning of life (zygote, embryo, foetus).

Do advances in medicine and intensive care raise doubts over the neurological standard?

Advances in medicine have not made the slightest difference to the reality and inescapability of death, even though they have complicated the determination of death in certain circumstances mainly to do with resuscitation.

Any new technologies and medical acquisitions will serve primarily to treat acute brain injury patients more effectively. For the time being, the enormous expectations created by regenerative medicine and stem cells, etc. have absolutely no influence on the clinical application of the neurological standard of death. Nonetheless, basic research and clinical applications will continue to be monitored on an ongoing basis in the hope that the current certain irreversibility of organic neuronal injury will change. In particular, a close link must be maintained between the neurosciences, treatment of acute brain injury and the neurological standard of death in research and clinical practice on the one hand with an ongoing ethical and moral reassessment on the other. This was also the sense of the concluding remarks of the document produced by the Council on Bioethics and recent pronouncements by the Pope. Any new argument and medical evidence must be analyzed in depth *in primis* using the scientific method to establish its solid basis and validity. The Harvard committee was the first open a collegial discussion involving experts in medicine, philosophy, law, ethics, etc. on the basis of the scientific acquisitions of the time.

How is the neurological standard of death applied in Italy?

Italy was among the first countries to incorporate into its national legislation the rules for the neurological determination of death. The first legal instruments were two ministerial decrees applying the 1957 law, which have allowed

kidney transplants from heart-beating donors to be carried out since 1975. These criteria were subsequently inserted into Law 644/75 but were confined to cadavers destined for organ donation, thereby repeating the error made by the Harvard document.

The need to amend the 1975 law stemmed from three critical points: 1) the now outdated parameters for the determination of death for the purposes of transplantation, 2) the role of relatives supplanting the deceased person's intent expressed in life, 3) poor health service organization. Discussion on the topic of interest (determination and certification of death) has not been hindered in terms of updating scientific criteria. The long and difficult part of the discussion has focused on the ethico-legal aspects of medical behaviour towards death. The drafters of the 1993 law deemed that unitary concept of death should be asserted even when death was caused by different mechanisms. Likewise, in the same conditions of death, procedures for the ascertainment of death ought not to differ for the purposes of organ donation. In the public mind this would finally have clarified the concept of "brain" death and quelled criticism on its use as a means to favour transplantation. After a difficult and sometimes heated debate, the fundamental conclusion was reached to separate the rules on the determination of death from any other legislation on donation and transplantation. The 1993 law therefore contains two major innovations:

- the definition of death
- mandatory standard procedures faced with the same conditions of death irrespective of any subsequent use of the cadaver.

Thanks also to capillary update and specific training network for doctors in intensive care units, the knowledge and technical skills involved in the neurological standard for determination of death have increased considerably nationwide.

According to national and international prospective studies at least 60-70% of all patients with acute brain lesion that died in intensive care presented all the clinical and instrumental criteria of the neurological standard of death. However, many of these patients die from cardiocirculatory arrest without application of the neurological standard of death. Prospective data collected in recent years by the National Registry of deaths with acute cerebral lesions in Italian intensive care units indicate that out of around 5500 deaths in all Italian intensive care units the neurological standard was applied in around 50% of cases and in 80% of these deaths was declared by a Medical Committee (around 2200/year). Organ donation for the purpose of therapeutic transplantation occurred in just over half of these cases (Procaccio *et al.*, 2008).

Among the complex "end-of-life" issues in intensive care, well-documented also by the recent findings produced by

the "GIVITI Project" (Italian Group for the Evaluation of Intensive Care Interventions) (Bertolini, 2007), the neurological determination of death is nonetheless a milestone shared in particular by intensivists. The neurological determination of death has become part of the cultural, clinical and organizational heritage of all Italian hospitals. The standard is applied in thousands of patients, irrespective of the possibility of organ donation, as a fundamental medical and ethical act due first and foremost to the patients and their families. The care process must always ensure patients receive prompt appropriate treatment from first aid to intensive care, as the premise for obtaining the best outcomes in terms of mortality and quality of survival. Due to an intractable increase in intracranial pressure and a progressive disappearance of cerebral blood flow, only patients with a devastating brain injury may develop massive brain infarction and an irreversible loss of all brain function in the presence of a beating heart and artificial ventilation. As stated above, the Italian 1993 law enshrined the clear-cut separation required between the determination of death and the possibility of organ donation. The same law and the 1994 Decree amended in 2008 make respect for and accuracy of the requirements compulsory and require a detailed clinical and medicolegal procedure approved by several specialists, and offer an abundant guarantee of completeness, accuracy and certainty in the determination of death by both cardiac and neurological criteria. The temporal sequence of some aspects of the death determination and declaration is as follows:

1. In Italy no single doctor is entitled to declare an individual dead on the basis of neurological criteria: when s/he recognizes the clinical and instrumental neurological criteria of death he is obliged to request the Health Authority to convene a Medical Committee of three specialists (*neurology, legal medicine and anaesthesiology-intensive care*).
2. The Committee unanimously:
 - a) checks the absence of potentially confounding factors requiring the absence of cerebral blood flow test to be performed (e.g. uncertain aetiology of brain injury, presence of CNS active medications, impossibility to make a full clinical examination, age less than one year);
 - b) ascertains the persistence of the clinical neurological standard for at least six hours (state of unconsciousness, absence of spontaneous breathing and any reactivity of the cranial nerves) and electroencephalogram (absence of cerebral electrical activity);
 - c) at the end of the period of observation the Committee certifies the patient's death. The time of death is the time in which the neurological standard was determined and hence when the period of observation started.

3. The individual's death is notified to the relatives by the doctor in charge who has already been informed of the observation procedure by the Medical Committee.
4. Only then will the cadaver be treated differently depending on whether the deceased is a potential organ donor or not:
 - a) organ harvesting will occur only after checking the will of the deceased expressed in life or non refusal on the part of the relatives;
 - b) if organ donation is not possible the body is sent to the morgue for possible autopsy and burial.

In both cases there must be maximum respect for the care and integrity of the cadaver.

Italy is certainly among the countries that have adopted extremely strict, detailed and cautious legislation and a set of rules and guidelines that have given way to a consolidated uniform practice. These clinical and legal resources safeguard against carelessness and incompleteness that could occur in a relatively deregulated system like that in the United States (Greer *et al.*, 2008), justifying a "methodological" rather than conceptual concern expressed by some US experts.

Italian legislation and practice have also fostered a marked improvement in communicating with families and in public knowledge and awareness of the neurological criteria for death.

In Italy the ethical and moral position of the Catholic Church carries considerable weight as seen from the in-depth detailed activity of the working group appointed by the Pontifical Academy of Sciences. In 2006 this working group outlined the reasons why the neurological concept of death is valid as a definition of death, reaffirming that "brain" death is not a *synonym* for death, it not *equal* to death, does not *imply* death, but **is** death.

A special situation regards the duration of the period of observation in children under the age of five years shortened from 12 to six hours in 2008 in apparent contrast with the recommendations of the National Council of Bioethics (1991) and the *Guidelines for the Determination of Brain Death in Children* (1987). Moreover, recent specialist literature (Koszer *et al.*, 2007) confirms that the recommendations expressed when cohorts were much smaller than they are today are useless.

It should also be specified that generally speaking Italian legislation has incorporated any scientific progress in the means of determining death by neurological criteria with absolute objectivity both when it was simplified and when it was made more complicated. In this case the determination of death in children was reviewed in 2008 abolishing an arbitrary extension of the observation period to 12 hours for children under five and to 24 hours for babies under a year, but confirming the obligation to test blood flow in all cases of death in babies under a year, an extremely cautious and effective rule.

Final remarks

1. Forty years since definition of the Harvard criteria, the neurological standard for determination of death maintains all its validity and acceptability. The biological and philosophical rationale underpinning the irreversible loss of brain function proves its equivalence with the death of an individual, even when circulatory function is prolonged. The term "brain death" should be abolished and replaced by the term "*death determined by neurological criteria*".
2. Some arguments criticizing the concept of death determined by the neurological standard are well-founded, especially the possibility that brain necrosis may not be total, in the sense of necrosis of all brain cells, and the partial unreliability of the concept linked to the brain as the exclusive indispensable organ integrating the organism as a whole. Nevertheless, such arguments do not detract from the substantial validity of the concept and the criteria for its application for the past forty years in the vast majority of countries.
3. The pathophysiological contradiction between the concept of death based on "*total brain failure*" including the brain stem and that accepted in the UK based on brain stem necrosis is only an apparent one. The irreversible loss of the capacity for wakefulness and hence consciousness, associated with the loss of the capacity for spontaneous breathing, are the essence of the two concepts and summarize the pathophysiological core of death, clearly differentiating it from any other clinical situation.
4. Death is the moment in which a human being is no longer an "integrated whole", before the biological activity in all cells and tissues permanently ceases. The irreversible loss of the capacity and possibility of awareness of the external environment and receptivity of stimuli and hence the intrinsic force and stimulus determining the *fundamental vital force* constitute the *rationale* and the *sufficient and indispensable condition of death*.
5. Nonetheless constant attention to any new argument, criticism and comment in the field of determination of death is necessary. In particular, the new borderline situations continually created by medicine and technology must be entertained and belong to the controversial sphere of "end-of-life" issues in resuscitation.
6. Strong emphasis must be placed on the clear-cut separation between the determination of death by neurological or cardiac standards as a medical, ethical and legal duty in all cases, and any other medical act such as possible organ donation for therapeutic transplantation.
7. Nowadays the *dead donor rule* cannot be avoided for organ donation not only for ethical, legal and social reasons, but also because awareness of the certainty of death before donation is the leading critical issue for

most citizens in deciding for or against donation. On the basis of data collected in many countries, the certainty of death remains the most important concern for relatives having to choose whether to oppose the will of their loved one or when such intent had not been expressed in life.

8. The determination of death by neurological criteria is currently a consolidated practice in Italian intensive care units flanked by a major fall in mortality rates for patients with acute brain lesion. This has a strong ethical, moral, but also purely clinical value and is a consolidated asset for Italian doctors, understood and widely shared by the population who are constantly given accurate and appropriate information.
9. Ongoing updates must be made to medical guidelines in the wake of technological advances, namely for the indication and methodology of confirmatory tests. A quality project, based on continuous personal training and audits must be put in place to maintain appropriateness, efficacy and efficiency in a very delicate area of medicine. In particular the utmost clinical and instrumental care must be reserved for the pathophysiological peculiarities of death in babies and children.
10. Clinical research in the field of treating patients with severe brain injury will yield increasing experience and pathophysiological knowledge on the passage from coma to death.

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The Italian version of this paper was published in *Trapianti*, **4**, 173-191, 2009.

Translated by Anne Collins.