CLINICAL ETHICS

The concept of brain death did not evolve to benefit organ transplants

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Although it is commonly believed that the concept of brain death (BD) was developed to benefit organ transplants, it evolved independently. Transplantation owed its development to advances in surgery and immunosuppressive treatment; BD owed its origin to the development of intensive care. The first autotransplant was achieved in the early 1900s, when studies of increased intracranial pressure causing respiratory arrest with preserved heartbeat were reported. Between 1902 and 1950, the BD concept was supported by the discovery of EEG, Crile's definition of death, the use of EEG to demonstrate abolition of brain potentials after ischaemia, and Crafoord's statement that death was due to cessation of blood flow. Transplantation saw the first xenotransplant in humans and the first unsuccessful kidney transplant from a cadaver. In the 1950s, circulatory arrest in coma was identified by angiography, and the death of the nervous system and coma dépassé were described. Murray performed the first successful kidney transplant. In the 1960s, the BD concept and organ transplants were instantly linked when the first kidney transplant using a brain-dead donor was performed; Schwab proposed to use EEG in BD; the Harvard Committee report and the Sydney Declaration appeared; the first successful kidney, lung and pancreas transplants using cadaveric (not brain-dead) donors were achieved; Barnard performed the first human heart transplant. This historical review demonstrates that the BD concept and organ transplantation arose separately and advanced in parallel, and only began to progress together in the late 1960s. Therefore, the BD concept did not evolve to benefit transplantation.

HISTORICAL ACCOUNTS OF THE BD CONCEPT

The earliest accounts concerning states resembling what would today be recognised as BD go back to the end of the 19th century, when several authors reported that, during an increase of intracranial pressure (ICP) in experimental models and in patients, respiration suddenly stopped, whereas the heart continued to beat^{7–13}.

In 1892, Jalland⁸ reported a case with a brain abscess, stating, "The marvelous way in which respiration returned after having ceased for some time, as the pus was evacuated, was the cause of surprise to those who were present at the operation." In 1894, Horsley¹⁰ stated that patients with cerebral haemorrhage, brain tumours and depressed fractures of the skull "die from respiratory and not from cardiac failure." Duckworth¹¹ reported that "some cases of cerebral disease in which the function of respiration entirely ceases for some hours before that of the circulation." In 1902, Cushing^{12, 13} stated that, "in death from a fatal increase in intracranial tension the arrest of respiration precedes that of the heart. Prompt surgical relief, with a wide opening of the calvarium, may save life even in desperate cases with pronounced medullary involvement." Although these papers provide early descriptions of the BD syndrome,^{7–13} their authors still considered cessation of respiration and/or heartbeat to be the signs of death.

In 1929, Berger first discovers and records EEG in human beings, which he termed "elektroenkephalogramm."^{14–22} Within a year, Crile *et al*²³ attributed "the cause of clinical death to the fall in the potential between the different tissues," and "the cause of the death of single cells or of tissue cultures to the fall in the potential on the cell membrane."

In 1938, Sugar and Gerard²⁴ temporarily occluded the carotid artery in cats and demonstrated the abolition of electric potentials in different brain regions with EEG, correlated with their resistance to ischaemia. In 1939, Crafoord²⁵ stated that death was due to "cessation of blood flow to the brain and nothing else." In 1900, Hill²⁶ had concluded from experiments that "total deprivation of blood immediately paralyzes the brain." These were striking accounts concerning the importance of cerebral blood flow in maintaining brain function.^{24–26}

At the end of the 1950s, neuroradiologists and neurosurgeons repeatedly reported the

It is commonly believed that the concept of brain death (BD) evolved to benefit organ transplantation.^{1–3} Nonetheless, a historical approach to this issue will demonstrate that both had an entirely separate origin. Organ transplantation was developed thanks to technical advances in surgery and immunosuppressive treatment.⁴ Meanwhile, the BD concept was developed thanks to the development of intensive care techniques^{5, 6}.

In this paper, we present a historical investigation into the development of the concept of BD in the 20th century compared with some key moments of transplant advances. We conclude that although nowadays BD and organ transplantation are fully related, the concept of BD did not evolve to benefit transplantation.

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Abbreviations: BD, brain death; ICP, intracranial pressure

angiographic findings in cerebral circulation in patients with apnoea and those who were in coma.^{27–32} In 1953, Riishede and Ethelberg²⁷ first reported this radiological finding in patients in coma, but they deduced that it was due to brainstem reflexes that altered the vascular tone. An important report came from Löfstedt and von Reis,²⁹ in Sweden, who, in 1956, described six patients in coma without any passage of contrast through the cerebral circulation. At autopsy, there was no obstruction of the cerebral arteries. The authors concluded that increased ICP, possibly in combination with vasospasm, was the most probable explanation for the x ray findings.

Two landmark accounts appeared in 1959. At the beginning of that year, Wertheimer *et al*³³ and Jouvett³⁴ characterised the “death of the nervous system”. Some months later, Mollaret and Goulon³⁵ coined the term “coma dépassé” for an irreversible state of coma and apnoea.

Wertheimer *et al*³³ and Jouvett³⁴ described “the death of the nervous system” and equated the condition with the heart–lung preparation of the physiologists. They went further to propose stopping the ventilator if death of the nervous system was diagnosed clinically and by “the repeatedly verified absence of electro-encephalographic (EEG) activity both in the cortex and in the diencephalon, and if resuscitative efforts have been given enough time, 18–24 hours” (translation by Settergren³²).

Mollaret and Goulon³⁵ described a condition of deep coma with no spontaneous respiration, no reflexes, polyuria and low blood pressure if norepinephrine was not given continuously, and the absence of all EEG activity. They pointed out that if the ventilation or the infusion of norepinephrine were stopped, the patient would rapidly die—that is, cardiac arrest would follow. Although the article by Mollaret and Goulon³⁵ was a breakthrough contribution to characterising the BD syndrome, they did not consider that their patients were dead.

In 1963, Alexandre adopted BD diagnostic criteria similar to those from the Harvard Committee and applied those criteria in performing the first organ transplant from a brain-dead donor.⁵

Also in 1963, Schwab *et al*³⁶ proposed that, “The total absence of EEG activity after 30 min of recording is most important evidence of death of the nervous system.” They went further than to recommend EEG as an ancillary test: they incorporated EEG findings into their diagnostic criteria, which were similar to those of the Harvard Committee,³⁶ Schwab was a Harvard Committee’s expert.³⁶ It seems that the Harvard Committee participants were not aware of the French contribution in this area. Hence, there were parallel approaches to the subject of BD.³⁷

In 1965, Frykholm in Sweden suggested that the ventilator should be stopped in patients with no cranial nerve reflexes, an isoelectric EEG, and no blood flow through the brain at angiography.³²

Two major medical events occurred in 1968. On 5 August, the 22nd World Medical Assembly formulated an essential statement on human death.³⁸ As a caprice of history, on the same day, the *Journal of the American Medical Association* published a landmark article, *A definition of irreversible coma*, the Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death.³⁹ The Sydney Declaration touched on key philosophical issues for understanding death, stating that “Death is a gradual process at the cellular level with tissues varying in their ability to withstand deprivation of oxygen.” This account went further to state that, with regard to clinical concerns, death “lies not in the preservation of isolated cells but in the fate of a person.”³⁸

The Harvard Report had momentous repercussions and constituted a breakthrough account, establishing a paradigm for defining death by neurological criteria.³⁷ After the Harvard Committee’s report was published, BD was widely accepted.^{5 40}

HISTORY OF TRANSPLANTATION

Ulmann,⁴¹ in January 1902, reported the first renal autotransplantation in a dog: grafting a kidney into the neck. In 1906, Jaboulay,⁴² connected sheep and pig kidneys to the brachial vessels of two patients who were dying of renal failure. Neither kidney worked, but these were the first transplants, albeit xenografts, that had been placed in humans. The techniques used to join the vessels together were those developed and described by Carrel,^{43 44} who is known as the founding father of experimental organ transplantation because of his pioneering work with vascular techniques.

In 1936, the Soviet surgeon Voronoy⁴⁵ reported the transplantation of a human kidney to a patient with acute renal failure. There was a major mismatch of blood groups and the kidney never functioned. Voronoy carried out six kidney transplants without success.^{45–47}

The modern era of clinical transplantation began in the early 1950s, highlighted by the contribution of Kuss *et al*⁴⁸, Dubost *et al*⁴⁹, Servelle *et al*⁵⁰ and Michon *et al*⁵¹ in France,^{48–51} and by Hume *et al*⁵² in Boston. Hume made an early attempt at allografting the kidney from an unrelated donor and the kidney functioned well, but only for a short period.

In 1954, Murray and his team carried out the first successful human organ transplant, taking a kidney from an identical twin.^{53 54} This was a landmark event in the history of transplantation. In 1962, Murray performed the first successful cadaveric kidney transplant.⁵⁵ In 1963, Starzl⁵⁶ achieved the first human liver transplant and Hardy performed the first lung transplant.⁵⁷ In 1966, Lillehei *et al*⁵⁸ and Kelly *et al*⁵⁹ carried out the first successful pancreas transplant. The development of immunosuppressive treatment played a crucial role in those early successful organ transplants attempts between unrelated recipients and donors.⁶⁰

Another milestone event in the history of transplantation occurred in South Africa, on 3 December 1967, when Barnard carried out the world’s first successful human heart transplant.^{60–69}

In those days, the surgical team brought a brain-dead donor into the operating room with the recipient for the removal; the respirator was then stopped, and everyone waited for the donor’s heart to cease to beat. Technically, therefore, those donors were not “brain dead” at the time of organ retrieval. Rather, they had been declared dead by classical cardiorespiratory criteria.⁵

Even when Barnard⁶¹ reported his first successful heart transplant, he stated, “As soon as the donor had been certified dead (when the electrocardiogram had not shown activity for 5 minutes and there was absence of any spontaneous respiratory movements and absent reflexes) The donor chest was then opened rapidly.”

SUMMARY AND CONCLUSIONS

This historical review demonstrates that the BD concept and organ transplantation had different origins and followed a parallel progression, which had an instantaneous conjunction in 1963, and finally joined and began to move along together after the Harvard Committee Report.^[39] Hence, the BD concept did not evolve to benefit transplantation, although it is impossible to deny that the final success of transplants was improved by the development and refinement of the concept of BD (table 1).

At the beginning of that century, when the first renal autotransplant was carried out, there were also several reports of increased ICP in experimental models and patients with ensuing respiratory arrest but with preserved heartbeat. From 1902 to 1950, the development of the BD concept was supported by the discovery of EEG, Crile’s definition of death,

Table 1 Keynote moments of the development of the brain death concept and transplants during the 20th century, in different periods, are comparatively presented

Transplants	Brain death concept
1902 First renal autotransplant	1902 Reports of increased ICP provoking respiratory arrest with preserved heart beat
1902–50 1906 First xenotransplant in humans 1933 First kidney transplant from a cadaveric donor, without success	1902–50 1929 Berger discovers the EEG 1930 Crile proposes a definition of death as a drop in electric potentials 1938 EEG is used to show loss of brain potentials after ischaemia 1939 Crafoord proposes that death in animals is due to the cessation of cerebral blood flow
1950–9 1954 First successful kidney transplant between identical twins	1950–9 1956 Cerebral circulatory arrest is demonstrated in comatose patients by angiography 1959 Death of the nervous system coma dépassé
1960–8 1962 First successful kidney transplant from a cadaveric donor 1963 First successful liver and lung transplants from cadaveric donors 1966 First successful pancreas transplant from a cadaveric donor 1968 First successful heart transplant between humans	1960–8 1963 First organ transplant using a brain-dead donor Schwab proposes to use the EEG for demonstrating death of the CNS 1968 Harvard Report and Sydney Declaration
CNS, central nervous system; ICP, intracranial pressure.	

the use of EEG to demonstrate abolition of brain electrical potentials after induced ischaemia, and Crafoord's statement that that death was due to "cessation of blood flow." This epoch was underscored in transplantation by the first xenotransplant in humans (1906), and the first kidney transplant from a cadaveric donor in 1933. From 1950 to 1959, several articles appeared about cerebral circulatory arrest detected by angiographic studies of patients in coma. Moreover, two crucial accounts emerged in 1959: descriptions of the death of the nervous system and coma dépassé. During the same period, Murray performed the first successful kidney transplant. In 1963, an instantaneous conjunction took place between the evolution of the BD notion and transplantation, when the first kidney transplant using a brain-dead donor was carried out. In the same year, Schwab proposed the use of EEG in establishing BD. In 1968, two landmark arguments for accepting BD appeared: the Harvard Committee Report and the Sydney Declaration. During this period, the first successful kidney, lung and pancreas transplants using cadaveric (not brain dead) donors were performed. Transplantation history was highlighted in 1967 with the first heart transplant between humans.

We speculate that if, in the future, the need for organs for transplantation from brain-dead donors is fully substituted by xenotransplants, the manufacture of tissues and organs by stem cell-derived techniques, or by other methods not yet known, the BD concept and transplantation will resume a parallel development.

In any event, in that time to come, when a patient is receiving life support, the physician will still need to face the thorny clinical state created by a non-functioning brain and a preserved heartbeat.

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