

# The first organ transplant from a brain-dead donor

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**Abstract**—In 1968, publication of the Harvard committee's report concerning “irreversible coma” established a paradigm for defining death by neurologic criteria (brain death [BD]). Five years earlier, Dr. Guy Alexandre, a Belgian surgeon, had not only adopted closely similar diagnostic criteria for BD but also applied those criteria in performing the first organ transplant from a brain-dead donor—a procedure many of his colleagues considered ethically unacceptable. To put those events into present-day perspective, the author reviewed the proceedings of a Ciba Symposium held in London in 1966 at which Alexandre introduced his pioneering view, obtaining information and documents from Alexandre and others who attended that meeting. Comparing Alexandre's approach with the Harvard report and later advances helps in understanding how both defining death by brain criteria and transplanting organs from a brain-dead donor have become morally tolerable today.

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At the beginning of 1959, Wertheimer et al. characterized the “death of the nervous system.”<sup>1</sup> Later that year, Mollaret and Goulon coined the term “coma dépassé” (beyond coma) for an irreversible state of coma and apnea.<sup>2</sup>

The Wertheimer article is not cited often, although it is a more complete clinical and neurophysiologic description of the syndrome than Mollaret and Goulon's.<sup>2</sup> Those were the first attempts to describe the condition of mechanically ventilated patients who have experienced the loss of brain functions but whose heartbeat continues.

The history of human organ transplantation had begun in 1954, when Joseph Murray, later a Nobel Laureate, and his team carried out a human organ transplant, taking a kidney from an identical twin.<sup>3</sup> In 1962, Murray performed the first successful cadaveric kidney transplant.<sup>4</sup> In 1963, Thomas Starzl achieved the first human liver transplant<sup>5</sup> and James D. Hardy performed the first lung transplant.<sup>6</sup>

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.<sup>7</sup> Technically, therefore, these donors were not “brain dead” at the time of organ retrieval. Rather, they had been declared dead by classic cardiorespiratory criteria.

It is commonly believed that the first set of criteria for brain death (BD) originated in 1968,<sup>8–11</sup> with

the report issued by the Ad Hoc Committee of the Harvard Medical School.<sup>12</sup> Wijdicks recently described the development of this document.<sup>13</sup> Actually, 5 years before the Harvard criteria appeared, Guy Alexandre, a Belgian surgeon at the Catholic University of Louvain, Belgium, introduced a set of BD criteria based on the description of coma dépassé<sup>2</sup> and carried out the first transplant in his country.<sup>12</sup> When Alexandre and his team performed the transplant, they did not discontinue mechanical ventilation and wait for the donor's heart to stop beating. Theirs was the first transplantation ever to make use of a heart-beating, brain-dead donor.<sup>14–17</sup>

To investigate this milestone event, I reviewed the little-known proceedings of a Ciba Symposium held in London, on March 9 to 11, 1966.<sup>18</sup> I also corresponded with Alexandre, Jean-Paul Squifflet (acting chair of the Service of Kidney and Pancreatic Transplants and Surgery of Endocrine Glands of Louvain University), and Sir Roy Calne (who provided important information and historical documents).

**Alexandre's personal history.** Guy Alexandre pursued a fellowship in surgical research at Harvard University, under Murray's supervision, in 1961 and 1962. He worked at the Peter Bent Brigham Hospital, directed by Francis D. Moore. His first contact in Boston was with Calne, who had also done a fellowship on Moore's service but who, at that time, was packing to return to England. Calne entrusted to

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*Table Alexandre's criteria<sup>18</sup> compared with Harvard criteria<sup>12</sup>*

Precondition	Precondition
Severe craniocerebral injury	Irreversible cerebral damage; exclusion of two conditions: Hypothermia (below 90 °F), CNS depressants such as barbiturates
Complete bilateral mydriasis	Pupil fixed and dilated and will not respond to direct source of bright light
Complete absence of reflexes, both natural and irresponsive to profound pain	Unreceptivity and nonresponsiveness to even the most intensely painful stimuli; ocular movement (to head turning and to irrigation of ears with ice water) and blinking are absent; no evidence of postural activity (decerebrate or other); swallowing, yawning, vocalization in abeyance; corneal and pharyngeal reflexes are absent; as a rule, tendon reflexes cannot be elicited; plantar or noxious stimulation gives no response
Complete absence of spontaneous respiration, 5 min after mechanical respiration has been stopped	No movements or breathing
Falling blood pressure, necessitating increasing amounts of vasopressor drugs: adrenaline or Neo-synephrine (phenylephrine hydrochloride)	Observation covering period of at least 1 h by physicians is adequate to satisfy the criteria of no spontaneous muscular movements or spontaneous respiration (established by turning off respirator for 3 min) or response to stimuli such as pain, touch, sound, or light
<6 h of observation if all five conditions are met	All of the above tests shall be repeated at least 24 h later with no change
Flat EEG	Flat EEG (when available, it should be utilized)

Alexandre the dogs surviving from his experiments.<sup>19</sup> Alexandre also worked with Hitchings and Eliot (Nobel Prize co-recipients) on various immunosuppressive experimental protocols.<sup>14,20-22</sup>

After his fellowship, Alexandre returned to Belgium and immediately initiated steps to make kidney transplantation feasible. On June 3, 1963, a patient with a severe head injury was brought to the emergency department of the Saint Pierre Hospital in Louvain, in profound coma. In spite of vigorous resuscitation procedures and the administration of vasopressors and other drugs, the patient showed the clinical picture of *coma dépassé*.<sup>2</sup>

At Alexandre's request, Jean Morelle, chair of the Department of Surgery, made "the most important decision of his career,"<sup>14</sup> allowing the removal of a kidney from that heart-beating patient. The graft functioned immediately after implant.<sup>14,15</sup> The recipient, who had been maintained by peritoneal dialysis, died of sepsis—with his new kidney in place—on day 87.

**CIBA Symposium on Transplantation.** The CIBA Symposium on Transplantation began to take shape when Michael Woodruff, from the Department of Surgical Science of the University of Edinburgh, pointed out to the Ciba Foundation's director, Dr. Wolstenholme, "the need for a small conference of medical men, lawyers, and others concerned in the ethical and legal problems of organ transplantation."<sup>18</sup> The conference, chaired by Lord Kilbrandon, had been organized originally without considering an invitation to Alexandre. Starzl had heard Alexandre's point of view concerning BD from Alexandre's colleague Otte, who was doing a year of specialized

training in Starzl's department. Starzl suggested that Alexandre should be invited (G.P.J. Alexandre, personal communication).

From that symposium came a book<sup>18</sup> that includes important lectures and also discussions among the delegates. Murray lectured on "Organ Transplantation: The Practical Possibilities."<sup>23</sup> A discussion followed, in which Alexandre expressed his pioneering opinion, remarking, "To throw some fuel into the discussion, I would like to tell you what we consider as death when we have potential donors who have severe craniocerebral injuries. In nine cases we have used patients with head injuries, whose hearts had not stopped, to do kidney transplantations. Five conditions were always met in these nine cases: 1) complete bilateral mydriasis; 2) complete absence of reflexes, both natural and irresponsive to profound pain; 3) complete absence of spontaneous respiration, 5 minutes after mechanical respiration has been stopped; 4) falling blood pressure, necessitating increasing amounts of vasopressive drugs (either adrenaline or Neo-synephrine [phenylephrine hydrochloride]); 5) a flat EEG. All five conditions must be met before the removal of a kidney can be considered."<sup>23</sup>

Alexandre therefore proposed one precondition (severe craniocerebral injury) and five criteria before BD could be diagnosed (table). If, by applying these criteria, the resuscitative team diagnosed the donor as being dead, the possible removal of the kidney was subsequently considered.

The meaning of an isoelectric EEG was fully discussed in the Ciba Symposium. Hamburger, director of the Claude Bernard Institute of Research and

Chief of the Renal Unit at the Necker Hospital in Paris, France, stated that he knew of two cases of coma due to severe barbiturate poisoning, with a flat EEG for several hours, followed by complete recovery.<sup>24</sup> He opined, "Those patients do not fulfill the other four conditions, nor do they have craniocerebral injuries, which I think is a very different situation."<sup>23</sup>

Murray then asked Alexandre, "Would you accept a flat EEG for 4 to 6 hours, along with your other four conditions, as incontrovertible evidence of death?"<sup>23</sup> Alexandre answered, "Using those five conditions you could not wait 6 hours, because falling blood pressure is one of the main conditions and after 6 hours the patients would already be dead anyway (conventionally dead). All our nine patients had blood pressures below 80 mm Hg after 30 or 45 minutes. They had had nearly half a liter of saline containing sometimes more than 160 mg noradrenaline to keep the blood pressure up."<sup>23</sup>

Alexandre considered that the fall in blood pressure was irreversible in his cases and denied that a patient in this state could be maintained for 6 hours. In recent years, it has been shown that, in some instances, human beings may have a long clinical existence after a declaration of BD, with preserved mechanisms for blood pressure control.<sup>25,26</sup> He added, "The only way of not cheating the potential cadaver donor is to have two separate teams: one working to resuscitate the patient and the other taking care of the transplantation."<sup>23</sup> The Harvard committee later defended this point of view.<sup>12</sup>

Revillard, from Lyon, France, then argued, "We look for those five signs, Dr. Alexandre, and two others: 1) interruption of blood flow in the brain as judged by angiography, which we assume is a better sign of death than a flat EEG, and 2)—of less value—the absence of reaction to atropine. We do not quite agree with you on the falling blood pressure because the fall may often occur later than the other signs, and in some cases the blood pressure remains at 100 mm for several hours."<sup>23</sup>

At that time, Revillard already considered an absence of cerebral blood flow (CBF) to be a more powerful sign of death than a flat EEG. Alexandre reported that in two of his cases, an angiogram showed that "the brain was not irrigated."<sup>23</sup> Bernat recently stated that complete absence of CBF provides the most certain evidence that global loss of clinical brain functions is irreversible.<sup>27</sup>

Hamburger added a remarkable endorsement of Alexandre's proposal.<sup>28</sup> "This new approach to the definition of death has a serious pathologic basis. We published in 1959 the case of a woman who had artificially maintained circulation and respiration but who otherwise fulfilled the criteria described by Dr. Alexandre and others. We asked our professor of neurology to examine her. . . . He said that this patient in his opinion had been dead for several days. Then after some time the machine was stopped because the heart had stopped. The autopsy was done

within an hour after this official death. Dr. Ivan Bertrand, who is one of our best pathologists of the nervous system, did the autopsy. The entire nervous system including the brain and spinal cord had the appearance of a nervous system when the autopsy is done 1 week after death. . . . The heart may not always be the only way of defining death."<sup>23</sup>

In spite of support for Alexandre's views from Revillard, Hamburger, and others, Starzl and Calne, world leaders in organ transplantation at that time, expressed their doubts about accepting Alexandre's diagnostic criteria.<sup>16,23</sup> Starzl offered, "I doubt if any of the members of our transplantation team could accept a person as being dead as long as there was a heart beat. We have been discussing this practice in relation to renal homografts. Here, a mistake in evaluation of the 'living cadaver' might not necessarily lead to an avoidable death since one kidney could be left. But what if the liver or heart were removed? Would any physician be willing to remove an unpaired vital organ before circulation had stopped?"<sup>23</sup>

Calne said, "Although Dr. Alexandre's criteria are medically persuasive, according to traditional definitions of death, he is in fact removing kidneys from live donors. I feel that if a patient has a heart beat, he cannot be regarded as a cadaver."<sup>23</sup> In a recent letter, Prof. Calne wrote, "I do very well remember the Ciba meeting on brain death in 1966. The main contribution of the meeting for me was Guy Alexandre's concept of *coma dépassé*. He pointed out that these criteria were used widely by neurologists as an indicator that further resuscitation and ventilation were fruitless and it was kindest to the relatives at this stage to tell them that with their consent ventilation would be stopped. Alexandre was, I think, the first to link this to the needs for transplantation surgery."

Starzl recently remarked, "At first, this idea appalled me because I envisioned that the care of a trauma victim could be jeopardized by virtue of his or her candidacy to become an organ donor. These fears were unfounded. The chances of a seriously injured patient being properly cared for were actually greatly increased when death was defined by the disappearance of brain function rather than the criteria of cessation of heart beat and respiration."<sup>29</sup>

In Alexandre's recent messages, he told me, "I always thought that the way cadaver transplantation was performed in these early days in the few centers that performed [it] was totally hypocritical. As you know, they brought the donor (then called "*coma dépassé*") into the operating room with the recipient. They prepared the donor for the removal of the organ and *then* stopped the respirator and waited for the heart to stop. My point of view was that if the donor was already dead, there was no need to damage the organ to be implanted by waiting for the heart to stop and to submit this organ to further ischemic damage." He also commented, "The five criteria we used evolved from the many discussions I had with my colleagues—dynamic persons

whose competence in the field of neurology did not suffer any critics. I also had the fortune of having a chief of Department of Surgery, Prof. Jean Morelle, who was competent in neurosurgery and well in favor of kidney transplantation and who was ready to accept the responsibility of the kidney removal from patients in coma dépassé."

I asked Alexandre if they declared the donor dead before the kidney was removed. He answered, "It is self-evident that removing a kidney from a heart-beating cadaver and allowing the reanimation team to stop the respirator once the kidney is removed . . . would not have been done unless the person was declared dead." He also remarked, "At the end of the Ciba symposium meeting you referred to, the president of the meeting asked the participants to let him know those who were prepared to act the way we were doing and to accept our criteria of brain death; I was the only one to raise my hand, all the others did not."

**Evolution of an idea.** Wijdicks, sketching the early history of BD, wrote, "There was little consensus and little published literature before 1968." He did not mention Wertheimer.<sup>1</sup> He alluded in passing to Alexandre's work: "In some modified form, these criteria [of coma dépassé] were mentioned at a transplantation meeting."<sup>13</sup>

Alexandre made his important decision to use a brain-dead, heart-beating donor only 4 years after the first characterizations of BD.<sup>1,2</sup> Although some Ciba Symposium delegates supported his notion, most rejected it.<sup>23</sup> Nonetheless, Alexandre had provoked a crucial discussion of the issue.

Murray, Alexandre's former mentor and co-author,<sup>20-22</sup> had attended the symposium. It would be hard to dismiss the idea that Alexandre's contribution went unremembered when the Harvard committee convened, almost exactly 2 years later. Wijdicks points out that the "available international literature was well known" to the committee.<sup>13</sup> Murray and Merrill, who were collaborators at Peter Bent Brigham, were both among the committee's members.<sup>13</sup> "In the literature," Wijdicks wrote, "there is a perpetuating concern that the transplant physicians on this committee played a decisive role in the definition of brain death with the intent to catapult their programs forward." He concludes, however, "I am uncertain after reading the documents whether an alleged agenda of facilitating transplantation through a new construct of death existed."<sup>13</sup>

The effort to separate the work of the committee from issues of transplantation, even though some members were closely associated with those issues in their work, is suggested by the article in the *Journal of the American Medical Association* that immediately follows the Ad Hoc Committee's: the report of the Judicial Council of the American Medical Association, "Ethical Guidelines for Organ Transplantation."<sup>21</sup> BD is not mentioned. The guidelines, however, include this: "When a vital, single organ is to be transplanted, the

death of the donor shall have been determined by at least one physician other than the recipient's physician. . . . In making this determination, the ethical physician will use all available, currently accepted scientific tests."<sup>21</sup> These details suggest that the Judicial Council had something beyond cardiorespiratory criteria in mind.

After the Harvard committee's report was published, BD was widely accepted.<sup>20</sup> Apparently, separating a new definition of death from using that definition to save lives helped it to gain support. Similarly, separating the responsibility for deciding, clinically, that BD had occurred from the tasks of transplantation added to the palatability of the new idea. As Moore emphasized, "How rapidly thinking has changed!"<sup>16</sup>

This article briefly indicates how a position that was at first morally suspicious became ethically acceptable in the course of a few years. Moreover, it documents Alexandre's bold, practical contribution to the global discussion of human death. Alexandre did, indeed, "throw some fuel into the discussion."

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