# Organ Transplantation and Society

# Organ Transplantation and Society:

## *A Critical Dilemma*

By

Félix Cantarovich

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# PREFACE

We live in the 21st century, and are accompanied by extraordinary advances in all aspects of medicine: experimental, technical, clinical-surgical, immunological, and preventive. We could consider that in some ways this magnificent opportunity for humanity involves the evolution towards and success of a seemingly unlimited future of surprising advances in the area of the transplantation of organs and tissues.

The current medical perspectives allow for achievements beyond the traditional initial possibilities of healing people with therapeutic means from the natural environment. After the discovery of these initial medical resources, a long path has been followed over time, incorporating the efforts to preserve the health and lives of patients made by those responsible for their well-being.

Following the continuous evolution in the 18th century, the roots of the pharmaceutical industry can be found in apothecaries and pharmacies that offered traditional treatments based on centuries of popular knowledge since the Middle Ages. At the end of the 18th century, the achievement of benefits for human health was based on the development of the therapeutic possibilities of natural products and the distribution of medicines elaborated by nascent pharmaceutical industries undergoing a constant evolution. However, the potential for a great revolution in modern medicine started perhaps with an almost-magical idea, concretized in a picture from the 13th century by Fra Angelico showing the first transplant between humans.

Organ transplantation has achieved, through surprising scientific advances, the ability to practically transform an inevitable death into a lasting useful life. The initial uncertain alternative of organ and tissue transplants required the vocation and efforts of different pioneers in different parts of the world. This effort crystallized in the mid-twentieth century, which is when the idea of the current medical practice of organ and tissue transplants began to be realized. The medical advances achieved in organ transplantation showed unimagined possibilities for successful alternatives, which increased day by day.

Currently, practically all solid organs can be transplanted, with marked success, because of the therapeutic and technical advances that are constantly being made. Without this privileged scientific progress, the terrible reality of terminal organ failure, only overcome in the case of renal failure by dialysis procedures, sooner or later leads to the deaths of patients.

The reality today is that the inexorable evolution of terminal organ failure can be eliminated by organ transplantation. However, this magnificent reality is simultaneously almost completely overshadowed by a persistently progressive critical situation: organ shortage. Because of this problem, the constant increase in the number of patients on waiting lists leads to permanently increasing patient mortality. These deaths are unfair!

The intention of this book is to carry out a critical analysis of the current global reality of organ shortages and its serious consequences for society. Because of the pedagogical need for a better understanding of this objective, a review from the historical beginnings of this new and significant evolution in medicine to the different alternatives of its progress has been done. The main objective is to describe and present the consequences of the current insufficient social behaviour towards donation, with the objective of carrying out an in-depth analysis of its causes. For these purposes and, particularly, because of the interest of this work for the general public, different personal concepts and proposals have been included. In addition, a selective analysis of the current literature on this subject has been performed.

Finally, this analysis of the organ shortage crisis allows a discussion of the results of several proposals to the never-modified social education programs, looking to achieve a change in the observable critical and insufficient behaviour towards organ donation.

In long lists hundreds of patients expect an organ that will allow them to live life in all its possibilities thanks to the prodigious advances of science in organ and tissue transplants. This new alternative of medicine is increasing progressively with the chronological changes in the prolongation of people's lives. This is why it is essential for society to understand that its education in the subject of organ donation is required in a comprehensive manner. This education includes understanding clearly the main role that everyone plays when it comes to organ donation: The pragmatic solution to the current world public health crisis where people are dying while waiting for an organ that society does not offer systematically.

Since the intention of this book is to reach society as a whole, to facilitate in readers not familiar with the medical-social sciences an easier understanding of the medical, technical and ethical-legal concepts of organ transplantation, some of the most important notions have been highlighted for pedagogical reasons.

On the other hand, given that summaries of the review data about the fundamental advances essentially linked to the professional practice of organ transplants have been presented in many cases, we have tried to complement the need for professional information with a comprehensive and updated bibliography.

—Félix Cantarovich

# ABBREVIATIONS

| | |
|---|---|
| Ag: | Antigen |
| ALS: | Anti-Lymphocytic Serum |
| AMR: | Antibody-Mediated Rejection |
| BD: | Brain Death |
| BEST: | Belatacept Early Steroid Withdrawal Trial |
| CIHI: | Canadian Institute of Health Information |
| CIT: | Cold Graft Ischemia Time |
| CNI: | Calcineurin Inhibitors |
| CsA: | Cyclosporine |
| CUCAI: | Single Coordination Center for Ablations and Implants |
| DA: | Donor Action |
| DCD: | Death Cardiovascular Donors |
| DDR: | Dead Donor Rule |
| DGF: | Delayed Graft Function |
| DSA: | Donor Specific Antibodies |
| ECD: | Expanded Criteria Donor |
| ECM: | Extra Cellular Matrices |
| ESRD: | End-Stage Renal Disease |
| HD: | Haemodialysis |
| HLA: | Human Leukocyte Antigen |
| IdeS: | Imlifidase |
| Ig: | Immunoglobulin |
| INCUCAI: | Single Central Institute Ablation and Implant Coordinator |
| IOM: | Institute of Medicine |
| KDPI: | Kidney Donor Profile Index |
| KPD: | Kidney Paired Donation |
| LKD: | Living Kidney Donors |
| LLDN: | Live-Donor Laparoscopic Nephrectomy |
| mAb: | Monoclonal Antibody |
| mAbs: | Monoclonal Antibodies |
| NHBD: | Non-Heart-Beating Donors |
| NHI: | National Health Insurance |
| NOTA: | National Organ Transplant Act |
| OPOs: | Organ Procurement Organisations |
| Opt-In: | Informed consent |
| Optn: | Organ Procurement and Transplantation Network |

| | |
|---|---|
| Opt-Out: | Presumed consent |
| OTA: | Occupational Therapy Australia |
| PD: | Peritoneal Dialysis |
| SCD: | Standard Criteria Donor |
| TTS: | The Transplantation Society |
| US: | United States |
| UAGA: | Uniform Anatomical Gift Act |
| UDDA: | Uniform Determination of Death Act |
| UNESCO: | United Nations Educational, Scientific and Cultural Organization |
| UNOS: | United Network for Organ Sharing |
| WHO: | World Health Organisation |

# CHAPTER ONE

# INTRODUCTION

## 1. Background

The field of transplant medicine holds unlimited potential for the betterment of society. However, because of the organ shortage crisis, continued evolution in this area is uncertain. Because of prejudices, ignorance, and misunderstandings, the individual moral responsibility to offer life to another human being is often avoided. The consequence of this conflicting situation is that patients waiting for organ transplantation are 'unfairly' dying every day. Surveys have shown that most people are willing to donate their organs or those of a family member after death but the reality is that in their grief, many of them ignore this commitment and their answer is negative (Cantarovich, 2019a; Volz & Szucs, 2011).

In general, the decision about organ donation, made when people are not facing the critical moment of death, is highly positive; as an example, in a survey in the United States, 94.9% of adults responded positively about their intention to donate their organs. However, people's behaviour changes when faced with death, particularly of a loved one; 2015 US statistics reveal organ shortage to be the major obstacle to making transplantations more accessible to a larger number of candidates. Only 30,973 transplants were performed from 15,064 donors while more than 121,000 candidates were waiting for a transplant. The critical consequences of this current attitude towards donation, causing harm to people's health and well-being, is a reality that undoubtedly constitutes a moral-ethical problem which requires serious reflections in the search for a solution (Department of Health and Human Services, 2013; Girlanda, 2016; Irving et al., 2012).

As a regrettable consequence of this situation, in the US, the evolution of mortality statistics in patients with end-stage renal failure is alarming. After adjustment for age, sex, race, comorbidity, and previous hospitalizations, the mortality of these patients in 2009 was 56% higher than in patients without this renal pathology. For patients with advanced stages, that is, practically in dialysis, the adjusted mortality rate is 76% higher. For

the thousands of people suffering the potential risks of dialysis, mortality related to the organ shortage reality should be considered an unjust death. This critical health problem undoubtedly requires an urgent solution (Pradeep, 2019).

On the other hand, there is an important relationship between the positive and negative aspects of donation and the socioeconomic, cultural and educational conditions of people which influences the behaviour of these groups regarding the donation of organs, primarily at the moment of death. Regarding transplantation ethics, society's maintenance over time of the mentioned deficiencies suggests an insufficient acknowledgement of the fundamental moral and ethical principles of organ donation and transplantation, brought on by education programs that have thus far been introduced yet never modified. Furthermore, in order to evaluate the benefits for public health budgets, people should know that organ transplantation will not only save the kidney patients on the waiting list but also provide substantial economic savings for the state's health programs. When kidney transplants increase, both patient lists and dialysis treatments decrease. The vital fact of transplantation, capable of saving thousands of lives each year, also represents for the US an elimination of dialysis treatments, a savings of approximately $46 billion per year. This result is even more valuable considering that the five-year patient survival rate following a kidney transplant is twice that conferred by dialysis (Salim et al., 2010; Loubeau, Loubeau & Jantzen, 2001; Held et al., 2016).

## 2. A review of transplantation history

The idea of replacing diseased or damaged body parts has been around for centuries. Transplantation challenges concerning skin and bones were attempted in ancient history and in the Middle Ages. For example, the successful transplantation of an entire leg was performed in the 13th century by St. Cosmas and St. Damian, physicians and saints, as imagined by the painter Fra Angelico and reproduced in several famous paintings. Skin grafts were achieved several centuries BC and developed further by Tagliacozi in the 16th century and, after that, at the beginning of the 19th century (Fracchia, De Jong, & Santing, 2013; Jerrom, 2015; Ménard, 2019).

In the second half of the 19th century, surgeons, with their greater anatomical knowledge, began to see the body as a compound of organs and tissues with specific functions. The use of surgery to remove diseased tissues and perform organ replacement seemed only a matter of time in the minds of these pioneers. Many years of experimental transplants—mostly

in animals but occasionally in humans too—eventually led to a miraculous moment of success. At this point, a fundamental issue of transplant medicine emerged: the exchangeability of body parts. Alexis Carrel's suture of blood vessels technique made it possible to link transplanted organs to their respective vascular connections in the host organisms. For his achievements, the French American surgeon was awarded the Nobel Prize in 1912, the second surgeon to be honoured in this fashion. Scientists began to use xenotransplants and allotransplants. In 1905, in New York, Alexis Carrel and Charles Guthrie performed the first heart transplantation in a dog. In 1906, Mathieu Jaboulay (1860–1913) in Lyon used kidneys from pigs and goats to attempt xeno-transplantations in human patients. The successful transplantations of bone and corneas came between 1900 and 1920. The first successful kidney transplant, involving identical twins, was accomplished in Boston in 1954 (Barker & Markmann, 2013).

Although consensus on the fate of homographs would not be reached for another 50 years, during the first decades of the 20th century, several well-known investigators established not only the inevitability of homograft failure but also most of the other basic principles of transplantation immunology. While experimenting with all kinds of organs and body parts it was observed that transplants could survive and function for an unlimited period but only if they were transplanted within the same animal. The conclusion made at that time was that living tissues must possess some biological individuality. The involvement of the immune system suggested the intentional suppression of the recipient's immune response as a way of making allo-transplants successful, and various methods were tried out. Assays of potential therapeutic antibodies, for example, were first produced by Karl Landsteiner in 1903 but abandoned after consistent failures (Nicholson, 2016).

A review of the great events that have favoured human society in the evolution of organ transplantation requires mention of the efforts made by illustrious scientists of the most remote antiquities. This comment is a tribute to them and a stimulus for new efforts to modify the frequently inappropriate behaviour towards organ donation and end the organ shortage dilemma.

## 3. Significant milestones in organ transplantation

800 BC: Indian doctors may have begun grafting skin from one part of the body to another to repair wounds and burns (Tomba et al., 2014; Jerrom, 2015).

1682: The earliest report of a bone-grafting procedure, in which the surgeon restored a bone defect using a cranial bone graft from a dog, was published in a book by Job Janszoo van Meekeren, a surgeon in Amsterdam. (Elsalanty & Genecov, 2009).

1700: In the early 1700s, Abraham Trembley and John Hunter became interested in grafting. Prophets in regenerative medicine, their efforts focused on tissue vitality, regeneration and adhesion (Evans, 2007; Lenhoff & Lenhoff, 1991).

1868: A skin allograft transplantation from one individual to another, by Swiss surgeon Jacques Louis Reverdin, was performed under anaesthesia and with the antisepsis postulates of Lister and Pasteur. This is remembered as the first human transplant (skin grafting). One of the numerous surgical instruments he designed, the Reverdin needle, has experienced a rebirth in recent laparoscopic surgery (Fariña Perez, 2010).

1881: The first clinical bone autograft was performed by William Macewen of Rothesay, Scotland. He used tibia bone slices excised from three donors to surgically solve a humeral imperfection in a three-year-old child. Successive clinical reports helped to establish the efficacy of autogenous bone implants for bone repair (Elsalanty & Genecov, 2009).

1902: Technically successful kidney transplants were achieved by Emerich Ullmann, who in 1902 performed an autologous transplant on a dog, and a dog and goat xenograft. Ullmann was the first to perform auto-homo and hetero-kidney transplants. In 1902, he also tried, unsuccessfully, to perform the first kidney transplant in a human (Druml, 2002).

1903: Paul Ehrlich was the first to describe the specific staining properties of leukocytes and other cell types. He was a pioneer in the formation of modern haematology and immunology as well in the development of chemotherapy and its therapeutic principles (Valent et al., 2016).

1903: Carl Olaf Jensen was the first to perform experiments in the area of transplant immunity. He revealed that spontaneous tumours in mice could be spread from one mouse to another. Through nineteen generations of grafts, he recognized that mice of different races were not all equally susceptible to the growth of tumours and suggested the concept of active immunity (Southworth Steen, 2018).

1906: The first transplant of a cornea was performed by Eduard Zirm, an Austrian ophthalmologist, who re-established the sight of a man blinded in an accident with lime burns, a difficult wound to treat even at the present time (Armitage, Tullo & Larkin, 2006).

1906: Jaboulay and Carrel developed the surgical technique through which vascular sutures can be successfully completed. This achievement at the beginning of the twentieth century would enable the ever-present medical desire to achieve through organ transplants a cure for terminal organ failure. Jaboulay's xenotransplant attempts in two patients with renal failure were unsuccessful (Watson & Dark, 2012).

1909: Ernst Unger, after performing more than 100 kidney transplants in animals, accomplished human transplants using en-bloc Macaccus kidneys, which failed within a few days (Barker & Markmann, 2013).

1909: Theodor Kocher verified that patients with a complete ablation of the thyroid gland presented in their evolution signs of hypothyroidism or childhood cretinism. For that reason, Kocher transplanted thyroid tissue in a patient who had undergone radical thyroidectomy. This original surgical intervention represents the equivalent of an organ transplant in the current meaning. Kocher was the first surgeon to win the Nobel Prize in Physiology Medicine, awarded in 1909, for his discoveries related to the functional activity of the thyroid gland (Kopp, 2009).

1912: Another Nobel Prize winner, Alexis Carrel, a former resident in the service of Professor Jaboulay, perfected his technique of vascular sutures using interrupted sutures. Carrel published his first articles on vascular anastomosis in 1902 with great success, and it is still a basic technique in current vascular surgery. Later, in the US and working with Guthrie, Carrel developed various methods for the anastomosis of small vessels. All his technical creations in vascular surgery have been fundamental in the development of organ transplantation (Sade, 2005).

1912: Georg Schöne may be considered the first researcher in the area of immunology. During his experience in the evolution of skin grafts in the Ehrlich laboratory, he noted that homografts always failed and that subsequent grafts from the same donor were rejected faster than those performed previously (Barker & Markmann, 2013).

1926: James B. Murphy showed that resistance to tumour homografts depended on the lymphatic system. He was convinced that lymphoid cells were responsible for the destruction of homografts. He tried to extend the

survival of the graft by eliminating the lymphocytes with irradiation, splenectomy, or benzol, the first historically used immunosuppressive chemical agent. As a result, he noted that these methods decreased lymphocytic infiltration in failed homografts. However, these studies and observations were for the most part not considered and, finally, they were practically forgotten (Barker & Markmann, 2013).

1930: Leo Loeb determined that the strength and timing of the rejection of skin homografts in rats were governed by the extent of genetic disparity between the donor and recipient. He also showed that lymphocytes were involved in rejection episodes (Barker & Markmann, 2013).

1933: Soviet surgeon Voronoy performed the first kidney transplant in humans using a six-hour anoxic cadaver kidney. The non-similarity of blood groups may have been the cause of the rapid failure of the graft. Four other human homograft transplants that Voronoy performed between 1933 and 1949 also failed (Matevossian et al., 2009).

1951: In Paris, René Küss developed a kidney transplant programme. The lack of dialysis treatments and the hundreds of patients with terminal renal failure justified this step, despite the lack of knowledge of how to manage the rejection problem. Eight kidney transplants were performed using the organs of guillotined criminals. No cadaveric transplant worked. The ninth transplant in this series was the first to use a living relative as a donor, the patient's mother. Unlike the others, this kidney functioned before experiencing an irreversible rejection by the third week. Küss's surgical technique is still used in kidney transplantation today (Starzl, 1993).

1954: The first successful kidney transplant was performed. Joseph Murray accomplished a living-donor transplantation between identical twin brothers. In the early 1950s, a series of kidney grafts was carried out at the Peter Bent Brigham Hospital in Boston, with some early graft function in certain patients (Yakubu et al., 2018).

1959: Mollaret and Goulon communicated a state of deep coma with no spontaneous respiration, no reflexes, polyuria, the absence of all EEG activity, and low blood pressure if norepinephrine was not given nonstop. They pointed out that if ventilation or the infusion of norepinephrine was stopped, cardiac arrest would follow and the patient would 'die'. Although French neurologists made an advance contribution to characterizing brain death (BD) syndrome, it is cited that they did not at that time consider that their patients were dead (Machado et al., 2007).

1959: Successful long-term transplants between nonidentical twins were accomplished in the US and France by Merrill and Hamburger. In practice, we should consider that these transplants initiated the general development of the current transplant programs. On this occasion, attempts were made to control the irreducible action of rejection in transplant evolution by using total-body irradiation. In this pioneering era, the risk of the ablation of a functional organ in a living donor, following the classical medical concept of 'primun non nocere', provoked moral, ethical, and religious controversy (Küss et al., 1962).

1960: The British immunologist Peter Medawar, a pioneer in the investigation of immunosuppressants in the control of rejection phenomena, received the Nobel Prize for his research into the discovery of acquired immunological tolerance. Medawar investigated the rejection of skin grafts by burn patients. Moreover, he studied the immune responses characterized by the infiltration of lymphocytes from genetically different grafts in comparison with autografts which were not rejected. These experiences helped to support the current successful transplant programs (Brent, 2016; Simpson, 2015).

1963: The first transplant involving a BD donor was performed. The first official BD criteria were developed in 1968 in the report issued by the Ad hoc Committee on Brain Death of Harvard Medical School. However, five years before the Harvard report, at the Catholic University of Louvain, Guy Alexandre performed the first transplant with a BD cadaveric donor, following the French description of 'coma dépassé' (Machado et al., 2007)

1966: The first attempt to cure type 1 diabetes with a total pancreas transplant was made at the University of Minnesota by Kelly et al. Previous pancreatic transplantation attempts had consisted only of segmental organ grafts, eliminating the exocrine function of the pancreas with an obstruction of the pancreatic duct with neoprene by Dubernard at Lyon, France. During the modern era of immunosuppression, the entire pancreatic transplantation technique, with the deviation of the exocrine function towards the digestive tract, became the gold standard for the simultaneous transplantation of the pancreas and kidney. The pancreatic transplant is available in three alternatives, specifically, simultaneous kidney/pancreas, the most frequent, or a pancreas transplant before or after kidney grafting; these alternatives represent the most effective functional therapy options capable of reversing metabolic abnormalities and preventing or minimizing many of the secondary complications of type 1 diabetes mellitus (Dubernard et al., 1978; Ferreira Meirelles, Salvalaggio & Pacheco-Silva, 2015; Becker et al., 2001).

1967: Thomas Starzl performed the world's first successful liver transplant. Starzl also carried out successful pioneering work to prevent organ rejection. Starzl was an innovator and an exceptional researcher and designer of the most transcendent progress in the practice of modern organ transplantation (Eghtesad & Fung, 2017).

1967: The first heart transplant was carried out; South African surgeon Christian Barnard courageously replaced the heart of a patient with advanced heart failure with the heart procured from a donor accident victim. Unfortunately, and with no sign of cardiac rejection, the patient died of pneumonia 18 days later. The emotional impact of this heart replacement impressed the world. Barnard performed a second transplant; in this case the patient led an active life for almost 19 months. It should be pointed out that some of Barnard's transplant patients reached a survival time of between 13 and 24 years. Separately, Barnard introduced the heart heterotopic transplant, an operation in which the donor's heart acts as an auxiliary pump. These inaugural heart transplants distinguish Barnard as a pioneer in cardiac surgery (Cooper, 2018).

1967: The first US heart transplant was performed by Adrian Kantrowitz at Maimonides Medical Centre in New York. The recipient was an 18-day-old male infant, who received the heart of a two-day-old anencephalic male. The procedure was carried out under hypothermia rather than cardiopulmonary bypass; it was technically successful, however, the patient died 6.5 hours after surgery from severe metabolic and respiratory acidosis (Silbergleit, 2006).

1968: Minnesota scientists relied on specific human histocompatibility system (HLA), tissue-matching, between a donor and patient to perform the first successful bone marrow transplant among non-twin siblings. At that time, it was known that the key to a successful transplant was a specific type of genetic comparison, known as HLA, between donor and receptor. A similar donor can help to prevent graft-versus-host disease. However, as many people do not have an HLA-compatible sibling, an unrelated HLA-compatible donor may be a possible alternative for transplantation (Khaddour & Mewawalla, 2019).

1968: The first definition of death based on neurological criteria was recognized by the Ad hoc Committee on Brain Death of the Harvard Medical School. The report, defining a detailed description of BD, had as its main purpose outlining irreversible coma as a new criterion for death.

This different death definition has since generated certain controversies for organ procurement in deceased persons (Beecher et al., 1968).

1968: The New England Organ Bank, based in Boston, was the first organ procurement organization responsible for enacting a flexible system for the procurement and distribution of organs for transplantation. The waiting time was considered the main criterion for the distribution of the procured organ and its allocation. This procedure also prioritized hyperimmunized patients and minority groups. The system was very adaptable to a variety of local situations (Kirkman, Milford & Luskin, 1993).

1971: The first successful lung transplant was reported by Fritz Derom in Belgium. The patient survived 10.5 months. The palliative benefit of the lung transplantation was rather questionable since the patient spent most of his post-operative evolution hospitalized. Pulmonary transplantation is complex due to the difficulty of keeping this vital organ in the best condition in the potential donor. Data from the United Network for Organ Sharing (UNOS) show that in 2012 only 21% of donor lungs were used due to lung injury due to direct trauma during maintenance in intensive care units, secretion aspiration, pneumonia, ventilator-induced lung damage, oxygen toxicity, and volume overload. These risk factors prevent the use of the lungs for transplantation (Yeung & Keshavjee, 2014; Grover et al., 1997).

1972: The discovery of the new immunosuppressive drug cyclosporine (CsA) presented significant possibilities in the suppression of acute rejection. Comparative trials between CsA versus azathioprine and steroids showed promising results, resulting in clinical approval for its use in transplantation in 1980. The introduction of CsA radically improved graft and patient survival, mainly in cases involving extra-renal organs. The introduction of new immunosuppressive treatments and the possibility of greater graft survival have also generated alternative research related to the long-term tolerance of transplanted organs (Ruiz et al., 2013).

1978: CsA was introduced in immunosuppressive treatments. Between 1982 and 1985, multiple multicentre trials showed the important progress achieved by this drug in the prevention of episodes of acute rejection, improving the short and long-term survival of patients and grafts, especially concerning heart and liver transplants. Nevertheless, its use evidenced its high nephrotoxicity. Consequently, induction therapy with polyclonal antibodies and, more recently, monoclonal antibodies, firstly OKT3 and at present anti-IL-2R and others monoclonals, circumvent these risks as well

as possibly delay the early post-surgery introduction of CsA or decrease post-transplant doses (Lloveras, 2004).

1978: Argentina passed Law 21.541, which was the first legal instrument regulating organ transplantation in Latin America and created the National Centre of Procurement and Allocation of Organs and Tissues. The initiatives regarding transplantation were generated by Professor Alfredo Lanari at the Institute of Medical Research in Buenos Aires in the '50s, who performed renal transplants shortly after the successful results in Boston and Paris. The concerns of Argentine medical staff about organ transplantation were considered by the authorities of the moment, and this law was structured and enacted in 1977. The Procurement and Allocation Coordinating Centre (CUCAI, currently INCUCAI) responsible for the National Transplantation Programme began operating in 1978. This nascent organism was organized and directed until 1990 by Félix Cantarovich, a medical professional trained in France (Wikipedia. El INCUCAI).

1979: The US Congress requested the President's Commission for the Study of Ethics in Medicine to investigate and define the uncertainty surrounding the definition of being dead. The Commission framed a uniform definition of death that included both the traditional cardiopulmonary and the BD criteria, suggesting that 'an individual who has sustained either (1) irreversible cessation of circulatory and respiratory function, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead' (Gray, 1995).

1980: The Uniform Determination of Death Act (UDDA) defines death as either the irreversible cessation of circulatory and respiratory functions or the irreversible cessation of all functions of the brain, including the brain stem. The US National Conference of Commissioners on Uniform State Laws formulated the Uniform Law of the Determination of Death. 'This law stipulates that an individual who has suffered an irreversible cessation of circulatory and respiratory functions or an irreversible cessation of all functions of the entire brain, including the brain stem, is legally dead'. This definition was approved by the American Medical Association in 1980 and by the American Bar Association in 1981. The accepted criteria for the determination of BD assess the function of the entire brain. The conceptual importance of evaluating the function of the brain stem is to ensure that a person who breathes spontaneously is not declared dead (Delmonico, 2010).

1981: The first combined heart–lung transplant was performed. A complete heart–lung block was removed from the recipient. Norman

Shumway and his team performed an operation that would result in a cardiopulmonary transplant and a remarkable recovery for a 45-year-old patient in the end stages of primary pulmonary hypertension (Reitz, 2011).

1984: As transplants became less risky and more prevalent, the US Congress passed the National Organ Transplant Act (NOTA) to monitor ethical issues and address the country's organ shortage. The supply of organs remains the most persistent problem in the field of organ transplantation. NOTA established a national system for identifying transplantable organs and ensuring fair distribution to recipients based on medical need. The act also encouraged the creation of methods to promote donation, such as donor identification cards and widespread advertising. Even so, the supply of organs remains far from satisfying the need. The law also established a centralized registry for the distribution and allocation of organs and tissues, concomitantly prohibiting the sale of human organs (Jonsen, 2012).

1986: The first successful double lung transplant was performed by Patterson and Cooper in a 42-year-old woman with emphysema. The technique used involved completely removing the patient's lungs. The recipient's heart and the donor's heart were not removed. This surgical procedure allowed for the use of the heart of the donor to solve the transplant need of another patient (Patterson et al., 1988).

1986: Cohen et al. in Toronto performed the first intestinal transplantation using CsA, but the patient only survived for 10 days. An extended survival of an intestinal transplant recipient was first accomplished in 1987 when a 3½-year-old girl lived for 192 days after receiving a multiorgan transplant (Todo et al., 1994).

1989: Pichlmayr in Hanover was the first to report a case involving transplanting a donor liver into two recipients. Faced with the constant organ shortage, fatally inexorable in the case of hepatic transplantation, this technique and its variations serve the principle of dividing the full liver into portions, each with an adequate vascular pedicle, bile duct and venous drainage, both slices with adequate functional liver mass. This procedure allows two recipients to receive part of a donated liver. This kind of liver transplant makes both liver parts, given the significant characteristics of spontaneous growth of liver tissue, apt to be viable for transplantation, maximizing the use of cadaver donor organs in children and adults. Furthermore, a split liver transplant approach was established even in living donors (Broering et al., 2004).

1990: The first successful living-donor lobar lung transplant was performed by Vaughn Starnes at Stanford University. A mother's right upper lobe was transplanted into her young daughter, who was born with bronchopulmonary dysplasia, and the patient survived. Living-donor lobar lung transplantation offers a survival alternative for patients with a life expectancy of less than a few months (Starnes et al., 1996; Venuta & Van Raemdonck, 2017).

1991: Surgeon General Antonia Novello convened a national workshop on increasing organ donations, with the participation of 123 experts in transplantation and education. Regarding the need for a greater social response to organ donation, potentially provoked through a more efficient education programme, this meeting was a response to the critical need for a comprehensive effort to save the lives of thousands of Americans waiting for available organ donors. It is interesting to point out in the analysis of this document and in relation to the intention of this work the importance given to the education of all levels of society, the stress on professional education, and particularly, the introduction of education programs in schools (The Surgeon General's Workshop, 1991).

Unfortunately, to date, these action proposals have not been successfully achieved.

1995: The first live-donor laparoscopic nephrectomy (LLDN) was performed by Ratner et al.; since then the LLDN technique has progressed to improve the safety of the donor and the outcome of the recipient. LLDN minimizes the drawbacks of live-donor nephrectomy, reduces post-operative pain, and shortens patient recovery by increasing the comfort of living donors (Ratner, Montgomery & Kavoussi, 2001; Gupta, Raina & Kumar, 2005).

1998: A team led by Jean-Michel Dubernard in Lyon achieved the first successful transplant of a hand and right forearm from a BD donor to a male recipient with a traumatic mid-forearm amputation (Dubernard et al., 1999).

1999: The first unilateral hand transplant in the US was realized in Louisville, Kentucky. After this assay this surgery was central to the subsequent successes seen in hand transplant centres around the world. However, some professionals and ethicists do not share the optimistic view of the safety and merits of transplanting a hand or limb. They consider that these body parts are not essential for life, and that the recipient needs to take, practically forever, high-risk drugs. Even if it is successful, they argue that the transplant can develop infections, cancer and other serious diseases

that may reduce the patient's lifespan and even lead to their death (Errico, Metcalfe & Platt, 2012; Nassimizadeh & Power, 2014).

2001: For the first time in the US, living donors exceeded the number of deceased donors. Due to the shortage of organs from deceased donors, living kidney donors have become a necessary resource for transplants. Perhaps the most controversial of all efforts to address organ shortages has focused on increasing the number of living organ donors. The concepts used to justify putting live kidney donors at some risk include the low danger to the donor, the favourable risk-benefit ratio in the donation, the psychological benefits for the donor generated by the altruistic action, and respecting autonomy through informed consent (Steinberg, 2004; Aulisio, DeVita & Luebke, 2007; Saidi & Hejazii Kenari, 2014).

Nevertheless, despite the value of these arguments, society must strive to reduce its growing dependence on living kidney donors by increasing the number of people giving their consent for their organs to be used upon their death, not achieved today due to the insufficient social motivation towards donation.

2003: The Organ Donation Breakthrough Collaborative was introduced by the US Department of Health and Human Services to increase organ donations in the nation's largest hospitals by implementing an intensive and highly motivated programme to promote the widespread use of best practices. In 2005, transplant centres joined the initiative with the goal of increasing the number of organs per donor. A reviewed version of the programme continues today as the Donation and Transplantation Community of Practice and is being managed by the Alliance, a private-sector donation/transplantation organization (Shafer et al., 2008).

2004: The Organ Donation and Recovery Improvement Act (PL 108-216) extended the authority of the National Organ Transplant Law to, among other things, make available the reimbursement of travel expenses and allowances for donors of living organs as well as grant subsidies in this regard to states and public entities (Warren et al., 2014).

2005: The Johns Hopkins Hospital in Baltimore pioneered 'domino chain' kidney transplants, joining incompatible living donor and recipient pairs by combining them with compatible pairs of unrelated couples so that each couple receives compatible organs. Kidney Paired Donation (KPD) is an unconventional approach that combines incompatible partners to achieve successful transplants, overcoming significant immune barriers. The KPD

exchange was first proposed in 1986 by Rapaport and gained popularity in 1997, when such transplants were ethically accepted. These exchanges between couples incompatible with their donors but compatible with a non-genetically related pair are currently a powerful ethically and medically convenient tool to increase the number of transplants. The results of KPD are comparable to those of direct live donations. National and international collaboration is encouraged to share these innovative strategies in order to increase the number of patients who can benefit from this possibility of overcoming the barriers of hyperimmunization (Malik & Cole, 2014; Irwin et al., 2012).

2005: The first successful partial face transplant was performed in France by Bernard Devauchelle, who was assisted by Jean-Michel Dubernard, at the Centre Hospitalier Universitaire Nord in Amiens. This revealed to the world that facial repair by transplantation is a superior surgical procedure compared to traditional reconstruction methods. The advances in vascularized composite allografts in recent years have been fundamental in achieving the current possibilities of face transplants. Nevertheless, as in the development of other organ transplants, this great progress in the current practice of transplantation has provoked controversies. The ongoing ethical debate about the candidate selection process, fundamentally structured in relation to concerns about immunosuppression, the high cost of the procedure, and the uncertainty of long-term aesthetic and functional results, still limit the worldwide application of facial transplantation (Kollar & Pomahac, 2018; Siemionow, 2016).

2008: The Stephanie Tubbs-Jones Life Gift Medal Act (PL 110 - 113) establishes the authority for the Department of Health and Human Services to issue a national medal in honour of organ donors. The main provision of this law establishes the following: The Gift of Life Donor Medal is a commemoration for the ‘heroes’ who gave the gift of life through the donation of the organs, eyes or tissues of their loved ones. These medals are presented to donor families to symbolize that their selfless decision to give those in need a chance of life will never be forgotten (Gift of Life Donor Program).

This law is undoubtedly a topic of interest that will be commented on in the course of this book.

2010: The first successful full-face transplant was carried out at Vall d’Hebron Hospital in Spain on a man injured in a shooting accident. The patient was discharged from the hospital four months later with partial-

motor recovery, no psychological challenges, and excellent acceptance of his novel facial look. By this time, several partial face transplants had already taken place around the world (Barret et al., 2011).

2016: A multicentre study validated the idea that patients who received kidney transplants from HLA-incompatible live donors had a substantial survival benefit compared with patients who did not undergo transplantation and those who waited for transplants from deceased donors (Orandi et al., 2016).

2017: New developments in molecular immunology and computational biology have increased the precision of donor- and recipient-matching in the contexts of both HLA and non-HLA compatibility. Individual omics-wide molecular diagnostics, extracorporeal therapies, and drug developments have allowed for more precise individual decision-making and treatment-tailoring to occur (Wekerle et al., 2017).

This analysis of the historical evolution of transplantation illustrates the prodigious adventure that this wonderful advance of medical science has had. Centuries of knowledge, starting in ancient times, have led to the uncontrollable progress of science, generated by the privilege of creative intelligence and the tenacity of the sometime heroic precursors of this current medical reality. From the fantastic conception of Fra Angelico in the thirteenth century, with the sacred experience of Saint Cosmas and Saint Damian, this premonitory historical revision has today become the miraculous era of organ transplantation, allowing death to become life, blindness light, deformity beauty and paralysis action. This legendary evolution of a medical activity apparently born of imagination transformed in time into a concrete reality of scientific knowledge and audacious medical practices that achieve surprising results for the benefit of patients. However, in recent decades, when scientific impulses and achievements reached an unimaginable zenith, we can see that the main engine of this overwhelming advance of science, humanity, has not practically modified its attitude to the donation of organs, creating, unfortunately, the current persistence of organ shortages.

Concerning the abovementioned Stephanie Tubbs-Jones Gift of Life Medal Act, offering a medal to the donor or to the family and thus rewarding organ donation as a ‘heroic decision’ deserves thoughtful analysis. This legal approach is without a doubt an expression of the relative success of social education programs that highlight the realization that organ donation represents a gift of life, usually for a stranger. We could rationalize that if

the essential conception of donation is to altruistically share the possibility of life to all, to consider this basically solidary action as heroic might not be applicable. In this sense, certain medical-legal solutions to overcoming the limited social attitudes towards organ donation certainly require profound constructive reflection.

## 4. Conceptual and ethical problems of organ donation and transplants

Organ transplants, and the necessary participation of society to achieve their fulfilment through organ donation, have raised several ethical and moral problems, mainly at the time of death of a loved one. Persistent organ shortage is both a medical and a social problem. The constant inadequate behaviour of many people is responsible for patients dying year after year while on the transplantation waiting list. This current ethical–moral problem demands a constant reflection on the part of decision makers planning education initiatives regarding health, including organ donation. Fundamentally, it is necessary to solve the critical dilemma of how to help those people who are on waiting lists, requiring the possibility of life. This can be done by addressing the strong inhibitions to donating that the general public have in the face of death. Principally, an ethical–moral question, not yet totally resolved on the social level and, in some cases, similarly unsolved among medical teams, is how to understand and accept the BD criteria (Dalal, 2015; Persad, Wertheimer & Emanuel, 2009; Abouna, 2008; Streba, Damian & Ioan, 2012).

Further, concerning the allocation of donated organs, Organ Procurement Organisations (OPOs) should strictly follow the principles instituted by Childress and Beauchamp. In the analysis of the ethical problems presented by organ and tissue transplants, it is of primary importance to take into account the four fundamental principles of bioethics they enunciated: (1) respect for autonomy, (2) absence of maleficence, (3) charity, and (4) justice.

1. The concept of respect for autonomy corresponds to the right of self-determination. The patient has the right to take or deny medical care, including the attention indispensable to preserving his life.
2. The principle of non-maleficence imposes doctors to preserve the patient's well-being.

3. The notion of charity requires practitioners to act in the best interest of their patients.
4. With respect to justice, basic concepts of ethics and morality must always be followed in patient medical practice.

(Beauchamp & Childress, 1994)

From a real point of view, all the above concepts simply mean that the medical interest must always be for the total benefit of the patient. The principle of justice refers to the obligations of honesty and integrity in doctor–patient relationships.

The shortage of organs created the possibility for medical groups that lack ethical and moral scruples, mainly in countries with populations in insufficient socioeconomic conditions and deficient in adequate laws or state organizations responsible for transplant programs, to create the so-called organs market. This inhumane traffic exploits people without resources and generates an imminent risk for the health of potential recipients who have the economic capacity to receive an organ from the regrettable and illegal offering of human body parts. The persistent organ shortage has resulted in the current serious reality of the so-called organ tourism, a sad alternative to the concepts of social justice and respect for human rights (Delmonico, 2009).

Taking these considerations into account, we will evaluate some of the most significant ethical–moral problems presented by the transplantation of organs and tissues.

**First:** Medical ethics have stipulated that it is essential not to harm people. Invading a healthy body and depriving it of a vital part might represent a kind of aggression toward the person that may deviate from the basic principles of medicine, i.e., the classic ‘primun non nocere’. Generally, the risk of extraction of an organ in the living donor is not negligible; however, in the case of renal transplantation, the risk of death is exceptional. Current data concerning operative mortality after donor nephrectomy is approximately three per 10,000 cases. A fully acceptable justification for this ‘medical aggression’, the extraction of a functionally healthy organ, is that it is in response to a fundamental social value which relates to saving or improving the quality of somebody’s life. However, the relative damage that could occur in the case of donation of an organ pair, such as the kidneys, is greatly exceeded by the possibility of offering, generally to a loved one, the alternative of a normal life. The lack of available organs has led to a significant increase in living donors. Although

this alternative partially resolves an obvious crisis, by partially resolving the need to increase the possibility of resorting to deceased donors, this solution runs the risk of perpetuating this serious medical-social problem (Lentine & Patel, 2012; Casares, 2010; Saidi & Hejazii Kenari, 2014).

**Second:** Living donors require, from the ethical–moral point of view, an evaluation of what donor consent means, considering the consequences of accepting the loss of a vital part of their body. One of the main problems concerning ethics in organ donation and transplantation refers to the legal regulations of consent and information given to people on the topic of the donation of organs (and tissues). The consent of the living donor must never be doubted. Concerning the validity of autonomy in the consent process, several ethical–moral questions have been outlined, specifically: Can one be sure that the consent is genuine? Can some people be forced to give their consent in a way that the screening process would not detect? (Wilkinson & Savulescu, 2012; Satyanarayana, 2008).

**Third:** A significant ethical concern involves distinguishing between a vegetative state and death. This complex topic was solved when French scientists described a new medical concept, the 'coma dépassé' (Machado et al., 2007).

**Fourth:** A current problem that should be mentioned is the use of donors presenting cardiocirculatory death (DCD). The advances in procurement and preservation techniques and the distressing problem of the ever-present lack of organs have generated this new ethical problem, which concerns patients who are subjected to intense treatment until, considered futile, it is eventually suspended, with the family's consent. In this case, the ethical problem involves establishing the necessary time to define death (Browne, 2010).

**Fifth:** From an ethical point of view, several arguments have been given to allow organ donation by people with a slight organic disability. These are basically utilitarian arguments considering that these potential donors lose less than the recipient earns. It has been suggested that this option would be plausible when donation is not a situation of significant risk, in which case organ donation would not infringe upon the 'do no harm' rule (Nygren, 2006).

**Six:** The correct assignment of priorities for allocating organs, procured from the always few necessary deceased donors, constitutes the primary ethical and moral responsibility of the organizations globally responsible for transplantation programs. These priorities are usually specified in the allocation programs of OPOs everywhere. In general, the primary organ