

# History of Solid Organ Transplantation and Organ Donation

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## KEYWORDS

- Organ transplantation • Kidney transplantation
- Lung transplantation • Liver transplantation
- Heart transplantation • Cyclosporine • Tacrolimus
- Immunosuppression • Organ donation • Organ allocation

Solid organ transplantation is one of the most remarkable and dramatic therapeutic advances in medicine during the past 60 years. This field has progressed initially from what can accurately be termed a “clinical experiment” to routine and reliable practice, which has proven to be clinically effective, life-saving and cost-effective when compared with nontransplantation management strategies of both chronic and acute end stage organ failures.<sup>1–3</sup> This remarkable evolution stems from a serial confluence of: cultural acceptance; legal and political evolution to facilitate organ donation, procurement and allocation; technical and cognitive advances in organ preservation, surgery, immunology, immunosuppression; and management of infectious diseases. The history of organ transplantation has also been laced with pure serendipitous discovery, tragic accidents, unfulfilled promise, abandoned paths, and incidents or practices that have produced legal or ethical quandaries; these features all combine to make the field a dynamic work-in-progress. Some of the major milestones of this multidisciplinary clinical science are reviewed in this chapter.

## ANCIENT HISTORY OF ORGAN TRANSPLANTATION

Humankind has always shown an interest in the removal of tissue from one site and placement to another site in the same person or different person as cosmetic, restorative or therapeutic procedures. Although not connected to the premodern or modern era of organ transplantation, intriguing descriptions exist in mythologic, religious, and historical literature including archaeological records that allude to the concept of tissue transplantation as far back as several millennia ago.<sup>4</sup> Hindu text from 2500–3000 BC provide detailed descriptions of using skin grafts crudely cut and molded from a patient’s own buttock or chin for reconstruction of noses mutilated

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by punishment for crimes committed.<sup>5</sup> Greek mythology alludes to gods, heroes and heraldic beasts with chimeric anatomy and abilities such as Chimera beasts. The Chinese physician, Pien Chiao, reportedly exchanged hearts between a man of strong spirit but weak will and a man of weak spirit but strong will to achieve a balance in each man. The New Testament of the Bible describes several instances that, in principal, would be defined as autotransplantation today. Jesus of Nazareth restored a servant's ear that had been severed in battle by Simon Peter's sword; Saint Peter reimplanted the breasts of Saint Agatha who was injured by torture; and Saint Mark reimplanted a battle-amputated hand of a soldier. In Jacopoda Varagine's *Leggenda Aura* (348 AD), the "miracle of the black leg" describes the replacement of the gangrenous leg of the Roman deacon Justinian with the leg of a dead Ethiopian man.<sup>6</sup>

Evidence for autotransplantation or allotransplantation of nonvisceral tissues, such as bone, teeth and skin, have been described as far back as the prehistoric Bronze Age. Temporarily removing bone segments from the skull to relieve brain swelling, a process called "trephination", is revealed in archaeological records from that period.<sup>7</sup>

Transplantation of teeth from one person to another is described over a broad range of history including ancient Egypt, Greece and Rome, during the Ottoman empire, and during the sixteenth to eighteenth centuries in France, Scotland and other western European sites. For example, the Dutchman Job van Meeneren successfully grafted bone from the skull of a dog to repair a skull defect in a human patient in 1668.

Such descriptions, although providing evidence of human inquisitiveness and resourcefulness toward improving the contemporary human condition, bear no literal relationship to the yet-to-emerge modern sciences that formed the actual knowledge and technical frameworks from which modern organ transplantation evolved.

#### PREMODERN ERA: 1900–1959

By the early twentieth century, successful transplantation of nonvisceral tissues such as human skin and cornea had already been reported.<sup>8,9</sup> The most important developments in this period include: experimentation with organ transplantation in animal models; attempted but failed kidney transplantation in humans; and observational but seminal discoveries pertaining to the timing, clinical manifestations, and immunologic mechanisms of allograft rejection in immunosuppressive-naïve recipients. Rapid advances in experimental and clinical surgical skills, including vascular anastomotic methods from the late nineteenth century into the early twentieth century, forged a knowledge and technical skill base upon which experimental visceral organ transplantation, principally kidney, could be performed in animals. The french surgeon Alexis Carrel perfected vascular anastomotic suturing methods, vessel reconstruction, and cold preservation. He also successfully performed kidney reimplantation in the neck of the same dog and a few years later between dogs; he won the Nobel Laureate Prize in 1912 while at the Rockefeller Institute for Medical Research.<sup>10,11</sup>

Despite technical surgical success, Carrel's consistent and sobering observation was that a hostile host response to the foreign allograft was the major residual impediment to successful animal and human organ transplantation:<sup>4</sup>

*"Should an organ, extirpated from an animal and replanted into its owner by a certain technique, continue to functionate normally, and should it cease to functionate normally when transplanted into another animal by the same technique, the physiologic disturbance could not be considered as brought about by the organ but would be due to the influence of the host, that is, the biological factors."*

This did not prevent several disastrous attempts at xenotransplantation (rabbit, pig, and macaque kidney) by French (M. Princeteau and Mathieu Jaboulay) and German (Ernst Unger) surgeons between 1905 and 1909.

Advances in transplantation knowledge and experimentation were initially slowed by World War I and the Great Depression. The field was re-invigorated with the increased need for skin allografting for severe burns and other battle injuries. Success, though, continued to be limited by rejection. Peter Medawar, a British surgeon who was assigned to investigate the mechanisms of skin allograft rejection, showed that serial full-thickness skin allografts in cattle were rejected more vigorously. He also found that skin grafts between monozygotic twins (fraternal) promptly thrived and were tolerated; this finding supported the concept that allograft rejection was an immunologic phenomenon with the classic immune properties of sensitization, memory and tolerance, all concepts which have stood to the present day.<sup>12,13</sup> These findings, coupled with subsequent experiments in rabbits that demonstrated that allograft rejection was modified with the administration of corticosteroids harnessed from the adrenal glands, formed the rationale for ultimately targeting the host immune system of allograft recipients.<sup>14</sup>

While discoveries in immunologic mechanisms of allograft rejection and innovations in technical aspects of surgery were being made, there were several precocious attempts at human kidney transplantation. In 1936, Voronoy, a Russian surgeon, performed a kidney transplantation from a blood type B cadaveric donor who had expired 6 hours previously to a uremic O blood type recipient.<sup>15</sup> The patient survived only 2 days and the kidney failed to produce any urine. Sixteen years later Kuss and Dubost, in Paris, harvested kidneys from convicts executed by guillotine.<sup>16,17</sup> The subsequent transplantations were technical surgical successes but still culminated in immunologic-mediated allograft failure and recipient deaths. A living, related mother-to-son kidney transplantation also performed in France with extraperitoneal placement of the donor kidney functioned for 3 weeks before the patient succumbed to rejection.<sup>18</sup>

From 1951–1952, Hume and colleagues conducted a series of nine kidney transplantations at Peter Bent Brigham Hospital in Boston, Massachusetts.<sup>19</sup>

In the first case, the graft was implanted in the recipient renal fossa, and in the next eight, the graft was implanted in the anterior thigh with urine draining via a constructed uretero-cutaneous drain. Although several patients received cortisone, all allografts were rapidly rejected. An earlier temporary transplantation effort in a young woman with renal failure following obstetric complications by the same surgeons was reported by Joseph Murray to have occurred as early as 1945.

In 1954, a seminal report by Dr. Joseph Murray and Dr. John Merrill at The Peter Bent Brigham Hospital, documented the successful transplantation of a kidney between living identical twin brothers (Ronald and Richard Herrick). The recipient, Richard, had been supported on an artificial kidney machine invented in Holland and modified at the Peter Bent Brigham Hospital (ie, Kolff-Brigham machine).<sup>20,21</sup> The procedure was both a surgical and immunologic success as the recipient survived 8 years with intact renal allograft function and no evidence of rejection before succumbing to cardiovascular disease. For his work, Joseph Murray won the 1990 Nobel Prize in Medicine (shared with E. Donnell Thomas for the first successful bone marrow transplantation). The same surgical team performed a similar operation between a female twin pair in 1956 with the recipient (Edith Helm) surviving into the 1990s.

The unprecedented allograft survival achieved in these particular cases compared with the dismal failures in the prior nonmatched pairs was no doubt secondary to

the opportunistic genetic matching of the donor and recipient without the aid of iatrogenic immunosuppression. Clearly, for the field to advance to a modern era and serve the genetically diverse general population needing organ transplantation, the development and refinement of immunosuppression, tissue typing and matching, and cadaveric organ harvesting and preservation would be needed.

## **EARLY IMMUNOSUPPRESSIVE ERA OF TRANSPLANTATION: 1960–1979**

### ***Application and Advances in Immunosuppression***

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Iatrogenic suppression of the recipient's immune system was the keystone to breaking the genetic compatibility barrier. At the Boston program in the late 1950s, conditioning recipients with sublethal total body irradiation was used in a series of ten kidney transplantations with nonidentical genetic lines.<sup>22,23</sup> Nine of ten patients expired within a month; however, the cause of death was not due to allograft failure but rather to the effects of radiation. However, one dizygotic (fraternal) twin recipient survived 20 years with intact renal function and this experience was also duplicated in Paris in another fraternal twin pair by Hamburger during the same year.<sup>24,25</sup>

It was becoming progressively apparent that cytoablative radiation was too blunt an immunosuppressive instrument, but it served as a "proof-of-concept" to the scientific transplantation community that a more refined and titratable modality, such as pharmacologic immunosuppression, posed an alternative possible pathway to success and safety. Fortuitously, collateral development of several antileukemia agents, including cyclophosphamide, methotrexate, 6-mercaptopurine and its analog azathioprine, was occurring during this time. Gertrude B. Elion and George H. Hitchings would share the 1988 Nobel Prize in Medicine for their contribution to the development of azathioprine in 1962. 6-mercaptopurine had already proved to delay skin graft rejection in rabbits and kidney graft rejection in dogs.<sup>26,27</sup> In 1960, the first renal transplantation managed with only pharmacologic immunosuppression (cyclophosphamide and methotrexate) was a female recipient of her mother's kidney.<sup>28</sup> Recovery of the recipient's bone marrow was accompanied by intermittent rejection managed with prednisone; however, the recipient expired after 143 days. In a series of ten kidney transplantations in the early 1960s that were immunosuppressed with either 6-mercaptopurine or azathioprine, there was only one 6-month survivor.<sup>23,29</sup> The resulting skepticism and pessimism about the efficacy of drug-induced myelosuppressive immunosuppression was short-lived. Landmark studies performed by Dr. Thomas Starzl in the early 1960s, while he was at the University of Colorado, showed that very high doses of prednisone (200 mg/d) added to azathioprine was able to reverse renal allograft rejection and induce host tolerance whereby the subsequent required immunosuppressive burden was diminished over time.<sup>30</sup>

The work of Thomas Starzl demonstrating the efficacy of a combination or "cocktail" immunosuppressive drug approach produced a frame-shift in organ transplantation on several fronts; it transformed kidney transplantation from a clinical experiment to an incipient clinical service using both cadaveric and live donors, led to a steady proliferation of transplantation centers of excellence in the United States and Europe, and opened the door for the first time to nonrenal organ transplantation including the liver, pancreas, heart and lungs, given the likely commonality of allograft rejection mechanisms across all organs. The development of rationed hemodialysis technology and vascular access led by Scribner during the 1960s also increased the potential pool of kidney transplant recipients by becoming the first "artificial bridge" to transplantation and, in the event of a failed allograft, as an alternative to death<sup>31</sup> Invariably, several sobering realities appeared during this immune barrier-breaking time period

appeared. These focused on the secondary complications of immunosuppression, such as infection and malignancy, although paradoxically these issues only became apparent due to the longer patient survivals.<sup>32–34</sup>

In 1967, in a remarkable paper titled “Death After Transplantation”, Starzl summarized the outcome of the first 125 organ recipients at the University of Colorado.<sup>32</sup> This patient group were immunosuppressed with a variable combination of irradiation, splenectomy, thymectomy, high-dose corticosteroids, and azathioprine. The first 60 deaths reported demonstrated a remarkably high rate of opportunistic bacterial, fungal, viral and protozoal infections, often multiple, and many of which were undetected and untreated ante-mortem. The dominant pathogen was cytomegalovirus as invasive disease was present in 30/60 (50%) of autopsies.

Because these findings were well before the development of many anti-infectives, preemptive and prophylaxis strategies, and sensitive monitoring methods, which were used in future decades, this report essentially portrayed the natural history of protracted corticosteroid-based immunosuppression in surgically complex patients. Opinion leaders in the more orthodox stream of medicine and surgery questioned the practicality and ethical grounds for organ transplantation.<sup>35</sup> This time period, as recalled by Starzl, reflected some of this opposing opinion: “As a consequence, transplantation acquired a renegade image, a burden soon compounded by difficulties in extending its reach to the replacement of vital organs other than the kidney.”<sup>1</sup>

Nevertheless, further advances in immunosuppressive pharmacology, customized to solid organ transplantation needs, were taking place. In 1966, the development of polyclonal antilymphocyte globulin (ALG) was synthesized from the serum of horses inoculated with human leukocytes.<sup>36</sup> ALG supplanted the limited practice of thoracic duct drainage to achieve lymphocyte depletion and was used only in a minority of kidney and liver recipients as part of a “triple regimen” with steroids and azathioprine.

It was the class precursor of future soluble anti-lymphocyte and anti-thymocyte polyclonal and monoclonal preparations, which became valuable adjuncts for the management of refractory rejection and, at some centers, as immunosuppressive induction.

### ***Liver Transplantation***

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Liver transplantation was developed only a few years after kidney transplantation. The first liver transplantation was attempted by Starzl at the University of Colorado in 1963, but it culminated in perioperative death of the patient because of overwhelming technical and hemorrhagic complications aggravated by severe portal hypertension and coagulopathy.<sup>37</sup> Between 1963 and 1967, liver transplantation was unsuccessfully attempted again in Colorado; Boston, Massachusetts; and Paris, France, resulting in intra- or early postoperative deaths and leading to a voluntary moratorium on further attempts. After resumption of efforts, the first one-year survivor of liver transplantation did not occur until 1967.<sup>38</sup> Initial attempts were unsuccessful because of a combination of technical difficulties and the unavailability of an effective means to prevent rejection. As increased experience was achieved, and with improvements in immunosuppression, prolonged liver recipient survivals were achieved. From 1963 to 1979, 170 patients underwent liver transplantation at the University of Colorado; 56 patients survived for one year, 25 for 13–22 years, and several remained alive with follow-ups of 17–31 years.<sup>39</sup> As with renal grafts, the long-term survival rate after liver transplantation remained poor (18%–30% one-year patient survival) until the advent of cyclosporine. Thomas Starzl also revived research efforts into xenotransplantation with a series of unsuccessful chimpanzee to human liver transplants between 1969 and 1973.

### **Other First Organ Transplantations**

Other organ transplantation “firsts” during this era included: the first heart transplantation by Dr. Christian Barnard in Capetown, South Africa in a cardiomyopathic recipient who survived 18 days; a pancreas transplantation in 1968 at the University of Minnesota; an unsuccessful lung transplantation in 1963 by James B. Hardy in a prison inmate with chronic lung infection who survived 18 days; and a heart-lung transplantation in 1968 by Dr. Denton Cooley at Stanford, California in a 2-month-old infant with congenital heart disease who survived only 14 hours.<sup>40–43</sup> The first successful heart-lung transplantation in a patient with primary pulmonary hypertension is credited to Bruce Reitz of Stanford University, in California, in 1981. The patient, Mary Gohlke, lived 5 years and co-authored a book, “I’ll Take Tomorrow” about her experience.<sup>44</sup> Despite the advances in drug-based immunosuppression and such pioneering first time transplantations, one-year graft survivals exceeding 50% were still not realized. However, an immunosuppressive agent that more accurately and effectively targeted the lymphocyte-based host response to the allograft was just on the horizon.

### **THE CALCINEURIN ERA: CYCLOSPORINE AND FK-506 (1983–PRESENT)**

The discovery of the immunomodulatory properties of cyclosporine by Swiss physician Jean Borel in 1977, its clinical investigational introduction in 1978, and its approval by the Food and Drug Administration as “Sandimmune” in 1983 were the most important immunosuppressive developments in organ transplantation.<sup>45–47</sup> This compound is a natural peptide product of the fungi *Cylindrocarpon lucidum* and *Trichoderma polysporum*.<sup>48</sup> Its potent immunologic effects are directed toward both cell-mediated T-helper lymphocyte and lymphocyte-derived antibody synthesis but without the bone marrow suppressive effect of azathioprine or the broad immune nonlymphocyte collateral effects of steroids.<sup>49</sup>

The increases in graft and patient survival when cyclosporine was part of a multidrug immunosuppressive regimen across all categories of existing solid organ transplantation was nothing short of stunning in the 1980s when 1-year graft survival rates exceeded 89% in kidney transplantation recipients and 70% in heart and liver transplantation recipients (**Fig. 1**).<sup>50–53</sup> In 1983, Joel Cooper of the Toronto General Hospital performed the first successful single lung transplantation on Tom Hall who was suffering from pulmonary fibrosis.<sup>54</sup> The patient lived for 6 years before succumbing to renal failure. Dr. Cooper extended his success to the first double lung transplantation in 1986.<sup>55</sup>

Significant adverse events were still common, particularly during the early part of the cyclosporine-related learning curve; they included: neurotoxicity, nephrotoxicity, opportunistic infection, de novo diabetes, and B-cell lymphoma. These complications were only partially responsive to dose-reduction strategies.

A major technical advance in liver transplantation during this period was the implementation of venovenous bypass circuitry that rerouted blood after venous clamping of the cava and portal vein in extracorporeal circuit back to the axillary vein to decompress venous congestion created by the cross-clamp of the portal vein and inferior vena cava at the time of native liver hepatectomy.<sup>56</sup>

In the early 1990s, FK-506 (tacrolimus) was clinically investigated in human liver recipients with cyclosporine-refractory rejection.<sup>57</sup> Approximately 75% of such allografts were rescued with the conversion to FK-506.<sup>58</sup> The sequential increment in both graft and patient survival in liver transplantation with the introduction of the calcineurin-inhibitors compared with the precalcineurin immunosuppressive era was impressive (see **Fig. 1**). Although many centers maintained some allegiance to

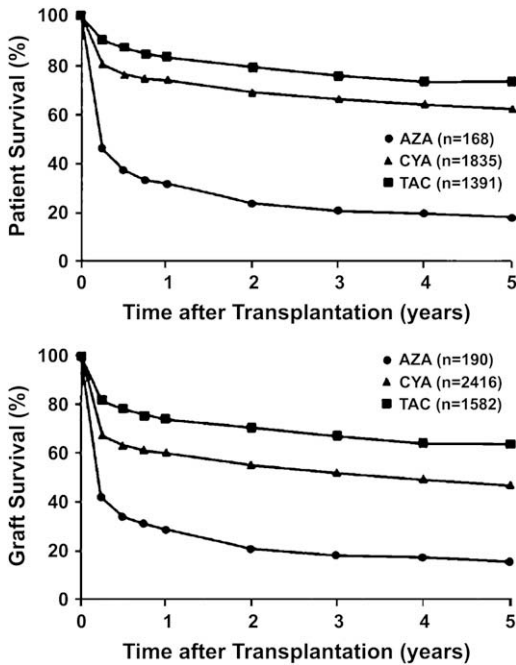


Fig. 1. Patient and liver allograft survival in the azathioprine, cyclosporine, and tacrolimus eras.

cyclosporine, the greater potency and equivalent safety of FK-506 compared to that of cyclosporine resulted in significant conversion to FK-506 based immunosuppression for liver, kidney, pancreas and thoracic organ transplantation.<sup>59–62</sup>

Intestinal transplantation, an endeavor that was abandoned in the 1970s, remained hampered by poor graft survival with cyclosporine. Many experts in the field at the time considered the bowel nontransplantable because of the high immunosuppressive burden required to suppress the host-response because of the bowel's high antigenic load and the converse problem of graft-versus-host disease. FK-506 provided a major boost to overcome the immunologic hurdle of intestinal and multivisceral transplantation in patients with short gut syndrome who were otherwise relegated to lifelong parenteral nutrition.<sup>63–65</sup> The first bowel transplantation occurred in conjunction with a liver transplantation at the London Health Sciences Center in 1988.

Novel immunosuppressive agents that also became available during this time, such as antilymphocyte drugs (OKT3 eg, Orthoclone, anti-thymocyte globulin eg, thymoglobulin), a new antiproliferative agent (mycophenolate mofetil), interleukin-2 receptor antagonists, and sirolimus, have increased the degrees of freedom for clinicians who may tailor a combination immunosuppressive regimen based upon the recipient's toxicity risks and degree of allograft tolerance.

### **Tissue Typing and Immunologic Methods**

Transplantation across the major blood antigen groups had long been known to result in rapid humoral-mediated rejection and failure of the kidney or heart allograft caused by the presence of preformed isoagglutinins that attacked the vascular endothelial resulting in vasculopathic necrosis.<sup>66,67</sup> However, successful liver transplantation

using a type O organ donor in a type A, B, or AB recipient can be performed—albeit with lower graft survival and hemolysis in the recipient. Successful liver transplantation had also been reported in the converse and more hostile antigen mismatch of an O recipient of a nonblood type O liver.<sup>68,69</sup>

Discoveries of the major histocompatibility complex (MHC) and the existence of human leukocyte antigens (HLA) occurred in the late 1950s. French physician Jean Dausset shared the 1980 Nobel Prize in Medicine for the description of the first known leukocyte antigen (now called HLA-A2) in 1958.<sup>70</sup> These key discoveries regarding immune function and graft rejection were not put into clinical use until the 1970s when a sensitive and rapid assay, the “HLA-crossmatch,” that could detect the presence of preformed lymphocytotoxic HLA antibodies in the recipient that were destructive to the renal and nonrenal allograft was developed.<sup>71,72</sup> Such sensitized patients might be prospectively managed with a more aggressive immunosuppressive regimen or other antibody depleting interventions, such as plasmapheresis.

What unexpectedly became clear over time, however, was that—unlike bone marrow transplantation where perfect HLA compatibility was required for marrow engraftment—a single or multiple antigen disparity in HLA matching did not create an insurmountable hurdle for graft survival amongst all the major organ categories. Thus, HLA-matching would not become a significant prospective eliminating factor for allocating donor organs to the prospective organ recipient.<sup>73</sup>

## ORGAN DONATION

A system for procuring large numbers of cadaveric donor organs was not a concern during the early years of clinical transplantation. As summarized above, a significant number of the earliest kidney donors were living donors because of the lack of refined immunosuppression and reliable preservation methods for the donated organ. Thus, the timing and process of procuring a suitable donor organ for transplantation was highly individualized in the earliest days of experimental organ transplantation. There is remarkably little information on the dynamics of identifying, consenting, and retrieval of the early cadaveric organs in the early clinical transplantation era in the 1960s.<sup>1</sup>

Important historical aspects within this realm include: earlier conceptions of death, modern and legal definitions of brain death and cardiac death, timing and techniques of organ procurement or harvesting, and organ preservation methods. The legislative landmarks that influenced the cadaveric organ donation process landscape are summarized in **Box 1**.

*Death and brain death: “a person is dead when a physician says so”  
—(Kenneth V. Iserson).<sup>74</sup>*

During its relatively brief modern history, human organ transplantation has been intimately tied to the legal definitions of brain death in the prospective organ donor. Prior to the early period of organ transplantation, a cardiorespiratory definition of death (defined as the cessation of detectable heartbeat and breathing) prevailed. Lazarus phenomena and even cases of premature burials were reported from the eighteenth to mid-twentieth centuries and amply highlighted the imperfection of such a concept.<sup>75,76</sup> With the increasing sophistication of mechanical, pharmacologic and other intensive care life support technology beginning in the mid-twentieth century, such an exclusive definition became more untenable. The technology to maintain organ perfusion and oxygenation created the patient–donor substrate from which cadaveric organ procurement could yield donor organs with recoverable ischemic injury and ultimately viable function for the recipient. This situation also

**Box 1****Major legislative and regulatory landmarks relevant to organ donation and transplantation in the United States**

- 1968 Harvard Commission defines “brain death”
- 1968 Uniform Anatomic Gift Act legalizes organ/tissue donation for transplantation
- 1971 Uniform Anatomic Gift Act mandates legality of donor card
- 1981 Uniform Determination of Death Act
- 1984 National Organ Transplant Act (NOTA) prohibits organ and tissue selling and establishes Organ Procurement and Transplantation Network (OPTN)
- 1986 Required Request Legislation
- 1986 United Network for Organ Sharing (UNOS) receives federal contract to ensure equitable access and organ allocation and oversight of procurement programs and transplant centers
- 1987 Uniform Anatomic Gift Act prioritized descendant’s wishes for donation over family wishes, requires hospitals to inquire about organ donation
- 1988 Joint Commission on Accreditation of Health Care Organizations (JCAHO) establishes requirement for hospitals to have identification and notification procedures to identify potential organ donors and referral for procurement
- 1991 Patient Self Determination Act
- 1996 Organ Donation Inset Card Act, authorizing mailing information about organ and tissue donation with income tax refunds
- 1998 National Conditions of Participation
- 1999 The Department of Health and Human Services issues “Final Rule” for Organ Procurement and Transplantation. Requests broader sharing of organs and more consistent medical criteria to be used for allocation. The goal is to make the allocation system fairer and to assure that patients with the most urgent medical conditions receive transplants.
- 2002 United Network Organ Sharing employs MELD scoring for liver allocation
- 2003 United Network Organ Sharing issues guidelines for extended donor criteria for kidney transplantation

produced both medical and ethical uncertainties for both potential organ procurement and/or continued life support.

Medicolegal efforts to standardize an alternate definition of death based on the absence of brain function began, in part, during the same time period that organ transplantation programs required clarity or a “dead-donor rule” to initiate an organ procurement process.<sup>77,78</sup>

The concept of brain death was introduced in 1968 by the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death whose requirement included unreceptivity and unresponsivity, no movements or spontaneous breathing, and no reflexes.<sup>79</sup> A flat electroencephalogram and ruling out reversible causes of loss of brain function, such as hypothermia or drug intoxication, were also recommended. The legislative complement to this working definition as it related to organ transplantation was the congressional passage of the Uniform Anatomic Gift Act, which made it legal to donate a deceased person’s organs and tissues for transplantation and reduced variations in legal guidelines the different states—although notably this failed to produce an increase in organ donation. Organ procurement for transplantation programs functioned through the 1970s with this first definition.

Further consensus and refinement was achieved with the President’s Commission in 1981 that defined brain death as “whole brain” and explicitly excluded nonbrain and

higher (cortical) brain criteria.<sup>80</sup> Quoted from this piece: “This view give the brain primacy not merely as the sponsor of consciousness but also as the complex organizer and the regulator of bodily functions...only the brain can direct the entire organism.”

The legal consequence of the Commission’s report was the Uniform Determination of Death Act requiring “irreversible cessation of all functions of the brain, including the brainstem”. Critics would argue that preserved neurohumoral function (antidiuretic hormone secretion from the posterior pituitary evidenced by the absence of diabetes insipidus) as well as rare cases of detectable electroencephalogram and evoked potential activity in patients meeting brain death criteria by clinical examinations made a whole-brain concept of brain death untenable.<sup>81</sup> Medical consultants to the same commission stipulated coma with responsiveness to any stimuli, standard bedside cranial nerve function tests, and an apnea test plus a specified time period after which such tests are repeated. Although this definition of brain death was generally accepted uniformly among physicians and became a legal definition throughout the United States, there remain significant cultural and religious variations in acceptance and understanding of the definition that hampered organ donation, despite the burgeoning success of transplantation in future years.<sup>82</sup>

### ***Organ Donation After Cardiac Death***

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The rising demand for cadaveric organs relative to a static cadaveric organ supply in the 1990s gave impetus to programs that deployed rapid procurement techniques after cessation of the heartbeat after elective withdrawal of life support in a patient with irreversible conditions and no contraindications for organ donation (controlled donation after cardiac death [DCD]) or rarely patients receiving cardiopulmonary resuscitation who may or may not be stabilized with cardiopulmonary bypass.<sup>83–86</sup> The transformation from a brain-death-only definition to a DCD-definition was and remains a major bioethical controversy. However, before the introduction of the brain death definition in 1968, this practice was how cadaveric organs were retrieved in the earliest days of clinical transplantation.

This practice has diversified the source of cadaveric organ donation, although brain death donation remains the dominant source of donor organs (Fig. 2).

In 2006, a special commission on DCD donation advocated the practice as “an ethically acceptable practice of end-of-life care, capable of increasing the number of deceased donor organs available for transplantation”.<sup>87</sup>

The DCD protocols varied across centers; however, a recent guideline from United Network of Organ Sharing formalized the serial components of donor identification, next-of-kin consent and approval, withdrawal of life-sustaining measures, pronouncement of death, and organ recovery are required.<sup>88</sup>

Kidney and liver organs have been the most frequent organs harvested from DCD donors, although rare reports of successful lung and heart retrieval and transplantation have been reported. Although renal transplant graft and patient survivals appear equivalent to patients receiving kidneys from brain-death donors, outcomes in DCD liver recipients have been consistently inferior across the same comparison with one-year graft survival rates of 72% between 2002–2007 compared with 84% one-year graft survival in brain death donors.<sup>89</sup> This result has dampened the enthusiasm for DCD liver donation in the last several years and increased the level of caution about which recipients should receive a DCD donor liver.<sup>89</sup>

Donor selection practices changed as a consequence of organ shortage. The time-less adage “necessity is the mother of invention” has always been the ethic in the field of solid organ transplantation, particularly as it pertains to organ supply. As of

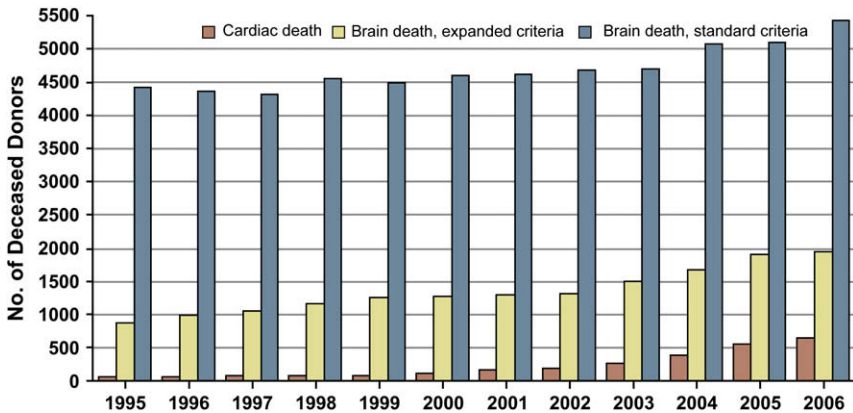


Fig. 2. Distribution of organ donation from brain death and cardiac death in the United States, 1995–2006.

November 21, 2008 there were 100,745 UNOS waiting-list candidates for organ transplantation in the United States; 8659 transplants were performed from 9490 donors during the first 8 months of 2008.<sup>90</sup> The increasing annual trend in the organ supply deficit for all organ transportation categories in the United States is shown (Fig. 3).

Cadaveric organ donation increased annually during the 1980s and 1990s because of increasing public education and awareness, the organization of hospital-based or free standing local organ procurement programs, and the sheer proliferation of transplantation centers. However, the list of patients who became transplantation-eligible rose at a much greater rate during the same time period. The margin of listed but

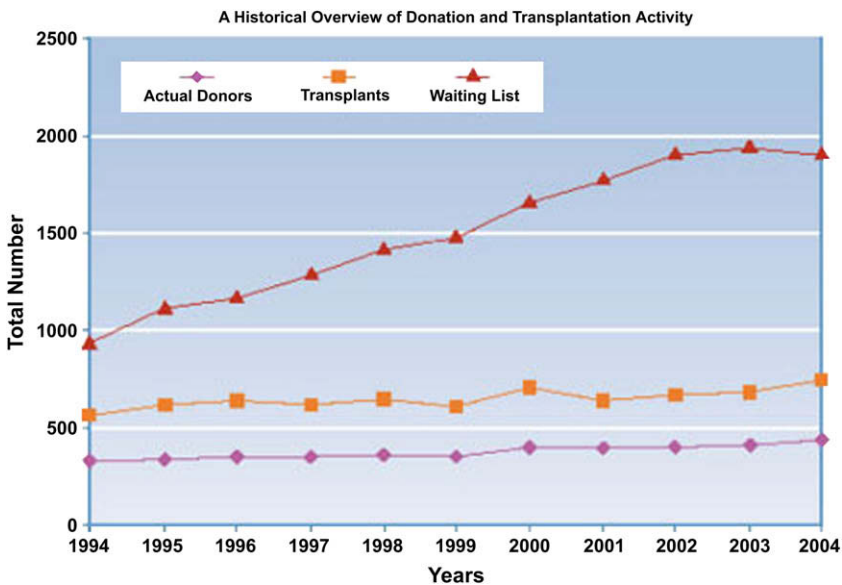


Fig. 3. United States organ transplant waiting list, transplants, and organ donors.

nontransplanted patients grew substantially and has become an area of public, political and medical concern and controversy.

In addition to DCD donation, several innovative practices emerged during this period to expand the finite and inadequate organ supply. Extended donor criteria for cadaveric organ donors were employed in high-volume kidney and liver transplantation centers.

In 2003, UNOS formalized extended donor criteria for kidney transplantation to include: donor age > 60 years and donors age 50–59 years with a history of stroke, hypertension, or a creatinine of greater than 1.5 mg/dL.<sup>91</sup> Prospective recipients of extended criteria kidneys needed to be informed at the time of consent that receiving an extended-donor kidney might increase the risk of poor graft function and other complications. Extended-donor criteria for liver transplantation evolved on a “by-transplantation center” basis with some variances across centers as to what defined an extended-criteria liver donor. A partial list includes: patient age, gender, race, weight, cause of brain death, length of hospital stay, prolonged warm or cold ischemia, donor hypernatremia, higher degrees of macrosteatosis, and the use of pressors.<sup>92,93</sup> Significant risks of primary nonfunction or delayed graft function has come with the use of such donors; this change is particularly critical because such organs are often paired with a recipient who is less severely ill.

Utilization of donors with positive serology for hepatitis C in hepatitis C positive recipients and hepatitis B core antibody donors in hepatitis B naïve and positive recipients, when coupled with post-transplantation hepatitis B antiviral treatment, have shown comparable graft and patient survival to seronegative liver donors.

Liberalization of donors with antemortem bloodstream infection and lung donors with infiltrates, when coupled with appropriate antimicrobial treatment of the recipient, have enhanced organ supply as well.

Live organ donation has its longest historical connection with kidney transplantation. Because of the increasing organ shortage and lengthening waiting times, living related kidney donation rose dramatically during the 1980s and 1990s to comprise about 50% of all performed kidney transplantation since 2000.<sup>90</sup> Advances in laproscopic-guided donor nephrectomy has no doubt also accelerated such practice.<sup>94</sup> Living donation has more recently expanded to liver, and partial pancreas, lung and small bowel donation that—due to the nature of the partial organ dissection and compromised residual organ reserve—have higher complication rates for the organ donor.<sup>95–97</sup>

Careful donor and recipient selection, technically perfect organ extraction, and meticulous postoperative care are obligatory to minimize donor jeopardy. A recent multidisciplinary consensus conference on the live organ donor was convened to provide guidelines to promote the well being of the living organ donor; donor complication rates are closely monitored by regulatory agencies.<sup>98</sup>

Other innovative strategies have evolved to expand the donor pool and shorten waiting list times. Directed living donation of kidneys across otherwise incompatibles related or nonrelated donor–recipient pairs has appeared in large transplantation centers that can accommodate a high operative work load in a short interval.<sup>99</sup> In situ or ex vivo cadaveric split liver transplantation allows transplantation of a left segment to a child and the remaining liver to a larger child or adult; this procedure has been successful but is risky because of the small split liver donor size and associated liver trauma.<sup>100–102</sup> Uncommonly, “domino” transplants are performed that use an organ from one recipient for subsequent transplantation to a second recipient in recipient disease states that permit such a strategy (ie, end stage liver disease due to a metabolic defect or amyloidosis).<sup>103,104</sup>

### ***Organ Procurement and Preservation***

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Removal of an organ from the body creates an obligatory ischemic insult whose sequelae may be subclinical organ dysfunction including delayed or permanent non-function. The role of temperature in its relation to organ ischemia was already known based on animal experimental transplantation that showed ischemia-sparing effects with the use of external iced saline or local graft arterial instillation of cooled fluids; hypothermic methods began to be applied in human kidney and liver transplantation.<sup>105</sup> Total body hypothermia of the living kidney donor during the donor nephrectomy was achieved with both external and internal cooling in the early 1960s. Core cooling was also employed before machine infusing into the distal aorta, an approach that was simplified later in the decade to aortic infusion of cooled crystalloid solution, a technique that persists to the present day.<sup>106–108</sup> Organ sharing across multiple centers and the rising success of all categories of organ transplantation after the introduction of cyclosporine prompted combined organ procurement of multiple organs en bloc or in sequence after in situ vascular cooling followed by ex vivo or back table dissection of the procured organs.<sup>109</sup>

Initial enthusiasm for ex vivo sanguinous or asanguinous artificial pulsatile perfusion for a period of up to 24–48 hours failed to produce significant improvements in allograft function, although interest and practice with modern devices have been rekindled in recent years for both cadaveric kidney and other organs.<sup>110,111</sup>

Organ immersion or the “slush” technique became the dominant standard of postprocurement storage from the 1980s to the present day.<sup>1</sup> A variety of flush solutions have been formulated; however, all have constituents to prevent cellular swelling, provide adequate osmolality, and acid buffering, inhibit auto-degradation of cell constituents, and promotion of metabolic recovery after reperfusion. The development of Collins solution, Euro-Collins solution, and University of Wisconsin solution were the major historical landmark advances in graft flush solutions. The latter, developed by James Southard and transplantation surgeon Folkert Belzer of the University of Wisconsin, Madison, has emerged as the preferred solution since the 1980s.<sup>112</sup> Upper limits of preservation time were extended to 48–72 hours for kidneys, 24 hours for livers, and 12 hours for hearts.

### ***Pitfalls and Perils***

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It should come as no surprise that with the accelerated volume of organ transplantation and the proliferation of many more transplantation centers and programs to serve the medical need, some unintended and unforeseen consequences have occurred, often with spectacular exposure in the lay media.

During the period of HIV-1 penetration into the general population and before the to the availability of HIV-1 antibody screening tests in 1985, a cluster of catastrophic case reports of HIV-1 transmission with rapid progression to AIDS caused by the high viral inoculum transferred to the recipient were documented.<sup>113,114</sup> Since the advent of HIV-screening, there have only been a few isolated cases of organ transplantation-related transmission.

Fatal transmission of rabies to four recipients from a donor dying of an enigmatic encephalitis after an undocumented bat-bite was proved only at the time of brain biopsy or postmortem in the recipients,<sup>115</sup> as was a similar transmission of West Nile Virus to four recipients who received organs from a polytransfused trauma victim.<sup>116</sup>

Accidental organ blood type mismatches caused by human error, although extremely rare, have resulted in rapid allograft failure and death in some cases. The last high profile case occurred at Duke University and involved the accidental

transplantation of a mismatched heart with consequential death of the recipient due to heart failure.<sup>117</sup>

Xenotransplantation to humans has been performed only a handful of times in the twentieth century with poor outcomes,<sup>118–121</sup> mostly using primate organs.

Although it is a fascinating and efficient way to expand organ supply, the unknown risks of xenozoonosis (particularly due to animal virus transmission), animal rights opposition, and the very high immunosuppressive burden needed to cross the inter-species immune barrier have made this field an appropriately slow and cautious work in progress.<sup>122</sup>

Many ethical questions continue to arise particularly related to promoting both cadaveric and living organ supply given the current limits of altruistic donation. Financial incentivization for both living and cadaveric organ donation has been a common practice in third world countries with emerging transplantation programs but no developed organ allocation system. Recently, a modified approach of indirect or direct compensation has been proffered by some in the United States, although concerns about exploitation, allocation fairness principles, and other potentials for misuse persist.<sup>123,124</sup>

The practice of obtaining organs from executed convicted prisoners in China has been long known and condemned by the global transplantation community.<sup>125</sup>

Because of organ shortages, refusal to transplantation caused by medical reasons, or the lack of local organ transplantation programs, individuals from other parts of the world have traveled to China for transplantation at their own expense. This practice has been termed “transplant tourism.”<sup>126</sup> Subsequent post-transplantation care has been met with resistance in the recipients’ native countries.

The battle amongst transplantation centers with competing interests for fewer organs has partially driven organ allocation policies in the United States. Basic to this dispute is whether to transplant the sickest patients or the less sick patients who inherently are more likely to survive the transplantation procedure and post-transplantation period.

This dynamic set large volume centers and geographic regions with a low organ supply against smaller transplantation centers and geographic regions with a higher organ supply.

In 2002, UNOS adopted the Model of Endstage Liver Disease (MELD), a scoring system using three objective parameters (bilirubin, serum creatinine, and international normalized ratio) that best predict short-term mortality. Subsequent analysis has shown indications that such a system results in better allocation by prioritizing patients at greatest need for a liver transplantation within organ procurement regions, although geographic disparities in organ availability and waiting times still remain unresolved.<sup>127,128</sup>

## SUMMARY

The history and advancement of organ transplantation to its current status is a remarkable collaboration of surgical, medical, legal, political and bioethical inputs over multiple generations and the foresight and diligence of pioneers in the field. The current stresses created by the increasing gap between organ supply and demand are in fact because of transplantation’s remarkable success rather than its failure. Existing and new challenges toward further improving outcome and access to organ transplantation will no doubt persist; however, there is little reason not to expect the same level of adaptive innovation to meet and overcome these realities.

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