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From Experimental Science to Clinical Medicine- A Historical Overview of Important Milestones in the Evolution of Organ Transplantation

Manik Razdan[1*] and Howard B. Degenholtz[2]

[1]Caring Health Center, 1049 Main St. Springfield MA 01103, USA.
[2]Health Policy and Management, University of Pittsburgh, Graduate School of Public Health, A748 Crabtree Hall, 130 De Soto Street Pittsburgh PA 15261, USA.

Authors' contributions

This work was carried out in collaboration between both authors. Author MR was involved in all areas of this project including literature search and manuscript write-up. Author HBD advised on the general direction of literature search, critically reviewed the manuscript and gave crucial input resulting in significant improvement in the quality of the write-up. Both authors have read and approved the final manuscript.

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ABSTRACT

The remarkable progress of transplant medicine in the latter half of the twentieth century has led to an unprecedented demand for donated organs that have historically remained in short supply. Although a clinically effective procedure, organ transplant's health benefit to the society is seriously limited by the shortage of organs. While the number of donors has been increasing at a steady rate, the number of people who can be effectively treated with a transplant has, far out-paced the supply of organs. It is therefore ironical that the benefits of transplant medicine are limited by the consequence of its own success. And it is this great paradox that makes this issue interesting and challenging. In this review, we briefly visit the historical developments that resulted in favorable conditions for the evolution of transplant medicine. The brief history of organ transplantation

**Corresponding author: E-mail: razdan@bu.edu;*

presented here draws attention to the rapid evolution of transplant medicine and the consequent rapid rise in demand for organs. This review is the first of the two-part series. In the second part of this series, we will recount how the society has responded to the increasingly evident need for transplantable organs, as well as, the ethical issues concerning removal of organs from the human body.

Keywords: History of organ transplantation; organ transplantation; HLA typing; organ shortage.

1. INTRODUCTION

The American story of organ transplantation is both remarkable and disappointing. From being an experimental medical procedure only a few decades ago, organ transplantation has evolved as the treatment of choice for end-stage organ disease. Yet thousands of lives are tragically lost to organ failure every year. In 2013 alone, 6,972 people died from end-stage organ disease in spite of abundant financial and technological resources available for transplantation [1]. Although a clinically effective procedure, organ transplantation's health benefit to the society is seriously limited by the shortage of organs. Each year, relatively few organs are transplanted, compared to the number of people with end-stage disease. In 2013, more than 120,000 patients were on the waiting list for an organ transplant but only about 29,000 transplants were performed from 14,250 donors [1].

The shortage of transplantable organs in the United States was apparent as early as 1988 when collection of organ transplant data had just begun. Fig. 1 presents the widening gap between demand and supply of organs for transplant. In 1988, there were 16,026 people waiting for an organ transplant but only 12,623 organs from 5,909 donors were transplanted with net shortage of at least[1] 3,403 organs [1,2]. By 2012, the number of organs falling short has increased to over 98,992 [1,2].

In addition, differing demand for various organs further adds to the complexity of the problem. Table 1 presents data on number of transplants performed and donors realized since 1998 (https://optn.transplant.hrsa.gov). Although renal transplant far exceeds any other organ transplant, demand for kidneys is also considerably higher than for other organs. Consequently, about eighty percent of candidates for transplant are waiting for kidneys.

While the number of donors has been increasing at a steady rate, the number of people who are eligible for a transplant has, far out-paced the supply of organs. It is therefore ironical that the benefits of transplant medicine are limited by the consequence of its own success. And it is this great paradox that makes this issue interesting and challenging.

In this review, we briefly visit the historical developments that resulted in favorable conditions for the evolution of transplant medicine. Why transplant medicine owes its remarkable progress in the past fifty years to a confluence of technological innovations in varied disciplines is discussed. The brief history of organ transplantation presented here draws attention to the rapid evolution of transplant medicine and the consequent rapid rise in the demand for transplantable organs in the United States. This review is the first of the two-part series. In the second part of this series, to be published in the subsequent issue of this journal, we will recount how the society has responded to the increasingly evident need for transplantable organs, as well as, the ethical issues concerning removal of organs from the human body.

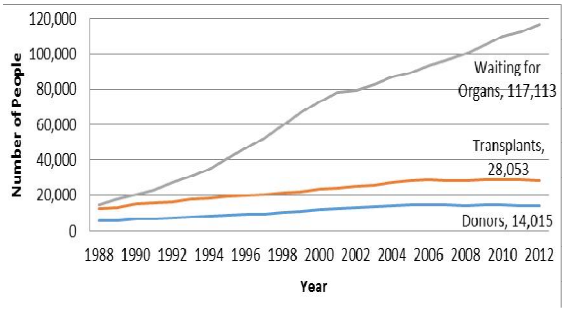

Fig. 1. Demand and supply of transplantable organs in the U.S. (1988 thru 2012)

[1] *The historical data on transplant waiting list obtained through request to OPTN show the number of candidates and not registrations waiting for a transplant. While each candidate needs at least one organ for transplant, some of these candidates may require multiple organ transplants. Thus in 1988, the 16,026 candidates on the waiting needed at least as many number of organs. Therefore after transplanting 12,623 organs, the organ deficit was at least 3,403. Organ deficit might be greater if there were some multi-organ transplant candidates on the waiting list.*

Table 1. Number of transplants performed and donors realized since 1988 (major solid organs)

Kidney	Transplants performed	Organ donors	Current waiting list
	420,118 (276,637 deceased)	**325,447 (181,918 deceased)**	**104,400**
Liver	147,658	161,788	14,557
Heart	68101	70,732	4,044
Lung	34,954	34,384	1,397
All	712,766	198,909	127,388

2. ORGAN TRANSPLANTS- FROM EXPERIMENTAL SCIENCE TO CLINICAL MEDICINE

The idea of transplanting body parts to restore bodily function and esthetics is not new. Examples of creatures with body parts from different species- referred to as chimeric beasts- are abundant in Greek mythology. The New Testament also contains several occurrences of auto-transplantation [3]. These occurrences include the story of the Jesus of Nazareth restoring a servant's ear that was sliced off by Simon Peter's sword during a battle. Other recorded accounts detail the stories of St. Peter replanting St. Agatha's breasts and St. Mark restoring a soldier's right hand that was severed in battle. An extraordinary description of a cadaveric allograft can be found in Legenda Aura. In the "miracle of the black leg", two saints replace Justinian's gangrenous leg with the leg of a recently buried Ethiopian man [4]. The oldest evidence of transplanting body parts dates back to the Bronze Age. Evidence of bone grafts being used to close the cranium post-trephination can be found in the archeological records from this age [5]. Detailed descriptions of using skin grafts to reconstruct amputated nose and damaged ears are found in the ancient Hindu texts dating as far back as 2500-3000 BCE [6,7].

Between 16th and 20th century, this ancient idea began to evolve into modern day transplant medicine. The few developments that occurred in this era are noted by Hossein Shayan [8]. An upper arm skin graft was used by an Italian surgeon for nose reconstruction in 1590s [8]. In the 17th century, teeth were successfully grafted in humans. A Scottish surgeon, John Hunter, had some success with Achilles tendon allografts [8]. By the beginning of the 18th century, experiments with skin and corneal grafts; thyroid, adrenal and ovarian grafts and other connective tissue grafts were reported [9]. In the 19th century, corneal and skin graft procedures made significant progress. In 1837, Samuel Bigger transplanted a full-thickness corneal graft into the blind eye of a gazelle [7]. In 1898, Winston Churchill was asked to donate some skin from his arm to an injured officer in a famous case of allogenic skin graft. Churchill's description of the incident in his own words alludes to the long-term success of the skin graft [7]:

> *"A piece of skin and some flesh about the size of a shilling from the inside of my arm. This precious fragment was grafted to my friend's wound. It remains there to this day and did him lasting good in many ways. I for my part keep the scar as a souvenir."*

With the arrival of the 20th century, a confluence of progressive and parallel developments in the fields of vascular surgery, physiology, immunology and pharmacology revolutionized organ transplantation from a mere subject of Greek legends into clinically effective medicine. Experimental models on animals, influential case studies and clinical trials with organ transplantation are reviewed in detail by Peter K. Linden and Thomas E. Starzl in their respective seminal articles [3,10]. Following a 1999 conference at the University of California, Los Angeles, a consensus paper identifying important historical milestones in the evolution of transplant medicine was published in the World Journal of Surgery [11]. The findings of the consensus conference were also summarized by Starzl a year later [12]. We briefly review those developments in science, technology and our understanding of the human body that brought a paradigm shift in transplantation science.

By the twentieth century, what Peter K. Linden refers to as the beginning of the "pre-modern era" (1900-1959), successful skin grafts and corneal transplants were being frequently reported [13,14]. The logical progression from this point was in the direction of organ transplantation. Animal studies on organ transplantation, failed renal transplantation in humans, innovations in vascular surgery and seminal observations in immunology characterize

this era. The main challenge with organ transplantation at the time was that organs are sensitive to ischemia and need major vessel anastomosis for vascular supply as opposed to skin grafts where capillary anastomoses are sufficient. Between 1902 and 1905, French surgeon Alexis Carrel refined the vascular anastomotic suturing methods, vessel reconstruction procedures, and cold preservation techniques [15,16]. With these innovations, it was now possible to surgically plant organs from one animal into another of the same species. However in ensuing animal transplant models, Carrel discovered that an adverse host response to the foreign graft was a hurdle in realizing clinical transplantation. As he famously observed [9]:

> *"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 physiological 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."*

Nevertheless renal transplantation in humans with allografts and xenografts was attempted in Russia and France- albeit with disastrous results [3,17]. The first breakthrough in the understanding of the host response to allografts came during World War I when the increased need for skin grafts for battle injuries steered Peter Medawar, a British surgeon, into investigating the causes of skin allograft rejection. He observed that skin grafts between monozygotic twins (identical twins- those who essentially share the same genetic code) were well tolerated [18]. Later in 1954, Joseph Murray and John Merrill reported a successful renal transplant between male monozygotic twins [19]. These findings suggested two things:

> 1) the host immune system had an important role in graft rejection; and 2) "*Iatrogenic suppression of the recipient's immune system was the keystone to breaking the genetic compatibility barrier*" [3].

Initial attempts at iatrogenic immune suppression employed cytoablative radiation. However it soon became apparent that this method was too crude to achieve meaningful health benefits as vast majority of patients died from the complications of total body irradiation such as infections and malignancy [20]. Development of antileukemic drugs promised a more refined method of suppressing the immune system. Pharmacologic immune suppression with prednisone was first tested on a female kidney recipient in 1960. The patient died after 5 months [21]. Immunosuppression with either azathioprine or 6-mercaptopurine also yielded poor survival rate with only one of the ten transplant recipients surviving to six months post-transplant [22,23]. The transplant revolution was halted until the early 1960s when Thomas Starzl at the University of Colorado demonstrated that high doses of prednisone with azathioprine could reverse graft rejection and even induce tolerance in the host [24]. Soon after Starzl overcame the genetic compatibility barrier, experimental renal transplants became clinical medicine although complications of lymphocyte depletion remained a problem [25]. A decade later, Borel & Stähelin discovered cyclosporine which was effective in immunosuppression but exhibited little cytotoxicity [26] and till date, combined with Starzl's "cocktail", this drug offers least harmful immune suppression [8].

Parallel to the development of pharmacological immunosuppression, advances in immunology led to the development of immunologic screening. In 1964, guidelines for ABO matching were developed to prevent transplanted organs from infracting due to ABO mismatch and resulting agglutination-related obstruction of microvasculature [27]. A year later, Terasaki et al. introduced the lymphocytotoxic crossmatch test to determine if the recipient's serum was presensitized to donor's lymphocytes [28]. Around the same time, Terasaki et al. also developed the Human Leukocyte Antigen crossmatch (HLA corssmatch) serum assay to detect preformed anti-graft HLA antibodies [29].

HLA typing was a crucial breakthrough in improving organ survival rates. Cell surface antigens on the transplanted organs are identified as non-self and elicit a strong immune response. Consequently, antibodies are produced that attack the transplanted organ resulting in failure. The principal cell surface antigen involved in graft rejection response is the major histocompatibility complex (MHC) molecule. The MHC protein molecules and their regulating HLA genes are typed into three classes. MHC Class I proteins are expressed on the surface of nucleated cells [30], class II proteins are found on the B lymphocytes,

activated T-lymphocytes, monocytes, macrophages etc. [30], and class III genes code for various components of the complement system [31]. MHC class I and II proteins have further subtypes, among which, HLA-A & HLA-B (MHC Class I) and HLA-DR (MHC Class II) have a major role in graft loss [32]. Interested readers are referred to Garcia et al. [33] and Sheldon & Poulton [34] for further details on the role of HLA matching in improving the graft survival rate.

Advances in organ procurement and preservation also contributed to the rapid rise of transplantation as a clinically effective procedure. In the 1980s, “flexible” surgical techniques for rapid removal of multiple organs were developed by Starzl et al. [35,36]. By 1905, Alexis Carrel had already pioneered the hypothermic preservation technique [16]. Further practicable advancements in organ preservation technology were made several decades later when the innovative yet logistically challenging machine perfusion technique [37] was replaced by the simple flush technique [38].

3. CONCLUSION

The remarkable evolution of organ transplantation is not unique. In fact rapid advancement in basic biomedical sciences and engineering and technology that were fundamental to the rise of organ transplantation also revolutionized medicine in general. However dependence on donated organs for transplants poses a challenge that is unique to this field of medicine. Indeed shortage of donated organs is proving to be an insurmountable barrier for the transplantation community. Consequently, the organ donation community continues to evolve as the demand for organs ever increases. In the second part of the two-part series, we will revisit the legislative and organizational changes that forged the organ procurement and transplant network into its present form.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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