



A Tale of Two Kidneys

Overcoming the Immunological Barrier in Organ Transplantation

By Roxanna Haghighat

Organ transplantation becomes a personal rather than scientific matter at the DMV's office, where newly-licensed drivers are faced with the crucial choice of whether or not to be an organ donor. Organ donation carries two seemingly polarized images—one of a grieving family choosing to give life to sick patients sitting at the top of the transplant list with no other treatment options and the other of the global organ black market by which scarce tissue resources are smuggled across borders. Perceptions aside, transplantation—while today a set of routine surgical procedures—remains an incredible scientific feat. The capacity to remove a live organ

from one person and implant it into a separate human being at the outset seemed overwhelmingly complicated and almost like science fiction—a more humanistic *Frankenstein*, perhaps. Yet, decades of research later and countless obstacles overcome, organ transplantation stands as the gold standard therapeutic approach for patients with failing organs.

While transplantation remains controversial in some cultures, as it is seen as commodification of human beings, the ability to perform organ transplants is a remarkable scientific achievement that is due largely to the efforts of Dr. Joseph E. Murray. During his time at the Peter Bent Brigham Hospital of the

Harvard Medical School (now known as Brigham and Women's Hospital), Dr. Murray performed the first successful transplant of a major organ, for which he received the Nobel Prize in Physiology in Medicine in 1990. More specifically, in 1954, he performed the first renal transplant between identical twins without organ rejection resulting in recipient mortality. Beyond this successful demonstration, Dr. Murray sought further to link his medical accomplishment to the basic scientific principles underlying it, investigating genetics, the immune system, and organ rejection. His discoveries, both in the operating room and at the bench, have forever opened up the possibility of a

curative therapy for end-stage disease.

The History of Transplantation

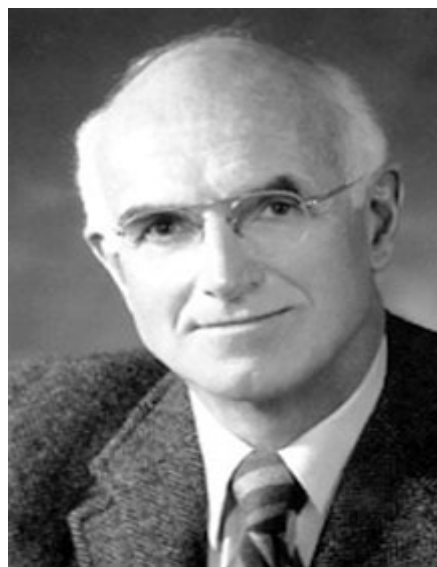
The first successful allograft—a transplant between individuals of the same species—was performed in 1682 (1). This crude operation, however, was limited to bone transplantation. Nearly two centuries later, the first human tissue graft was performed in Switzerland, but advancements to full, solid organ transplants consistently failed throughout the early 20th century (1). The first meaningful step toward a successful organ transplant was the allograft of a cornea in Austria in 1905; inspired by this success, surgeons in France began attempting kidney transplants beginning in 1906. Of a total forty patients, all passed away due to organ rejection, usually within the first year, which stymied physician willingness to perform and patient willingness to receive such an operation (2).

Given the repeated failures of these transplants, in 1912, French surgeon and Nobel Prize Laureate in Physiology or Medicine Alexis Carrel realized that there must be some “biological force” inhibiting a successful operation between individuals of the same species: “Cells are specific of the individual to whom they belong. This peculiarity of our body has so far prevented the wide

use of the transplantation of organs for therapeutic purposes.” (3). Given the limited understanding of the immune system at the time, this conclusion, attained through his extensive experience with grafts and transplants, is especially remarkable. Carrel himself had pioneered the first vascular suturing technique, known as “triangulation,” which entails connecting blood vessels from the living recipient and deceased donor (3). This method, inspired and perfected by his work with a seamstress, enabled the short-term success of organ transplants. By the late 1940s, fellow Nobel Laureate Sir Peter Medawar expressed the frustration of physicians towards the seemingly insurmountable challenge of transplantation, declaring that the biological force described by Carrel would “forever... inhibit transplantation from one individual to another” (4).

The Immunological Barrier

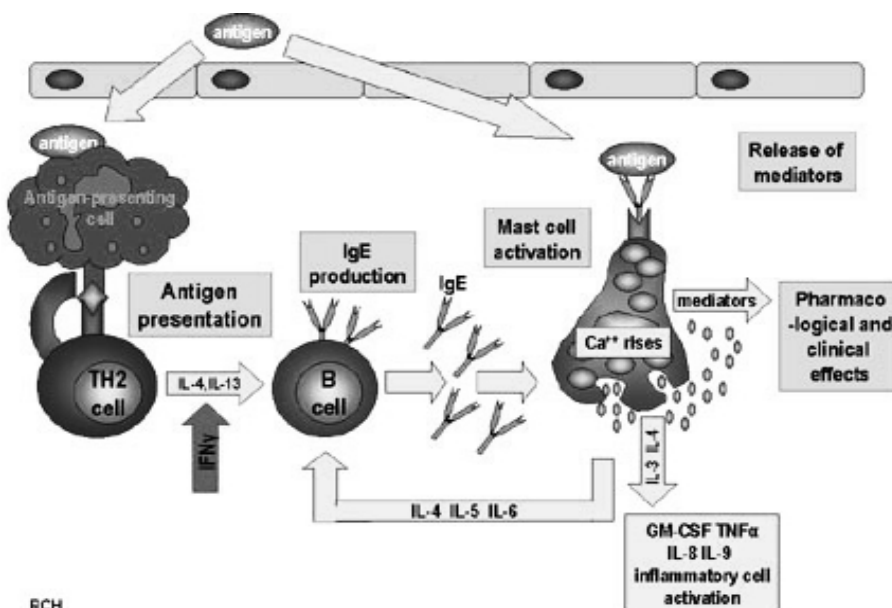
Yet, following a common thread in the history of medical advances, physician scientists refused to accept this ultimatum; instead, in the 1950s and 1960s, research uncovered the source of immune rejection, known as HLA antigens (Human Leukocyte Antigens). In particular, after clinical experience in France with hematology and research at Harvard Medical School, French



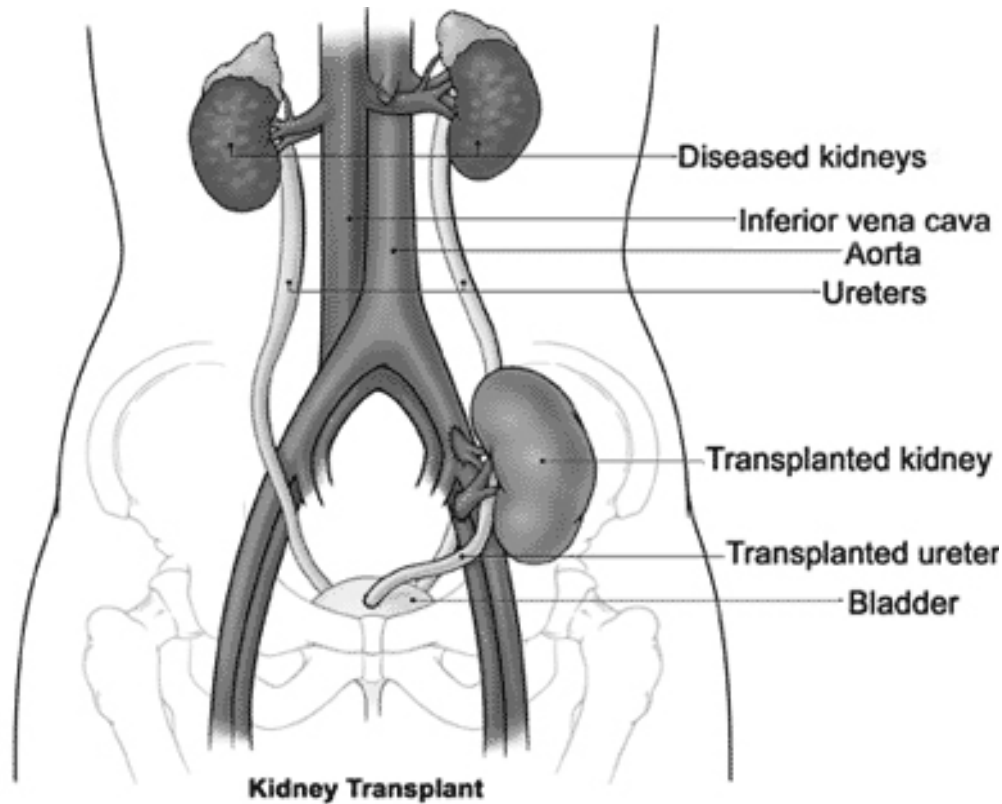
▲ Figure 1. Dr. Joseph E. Murray

immunologist Jean Dusset attempted to transfer techniques in immunohaematology, or blood banking, to white blood cells and platelets (5). After observing the agglutination of leukocytes and thrombocytes, he eventually identified the first leukocyte antigen in 1958, known as HLA-A2 (Human Leukocyte Antigen), for which he received the Nobel Prize in 1980 (5). The recipient's immune system recognizes the HLA antigens on the cell surfaces of the donor's organ, which induces the host cells' immunological response to reject the foreign cells. This process, known as the “graft-versus-host” reaction (GVH), underlay the failure of previous transplantation attempts.

The discovery of Carrel's infamous “biological factor” immediately sparked renewed interest in transplantation, especially in the field of nephrology. With the help of Dr. Carl W. Walter, Dutch physician Willem Kolff developed the first “artificial kidney,” or dialysis machine, in 1948; however, dialysis treatment was not only temporary but also expensive and painful (6). The lack of permanent therapy for patients with renal disease beckoned plastic surgeon Dr. Joseph Murray to



▲ Figure 2. A basic overview of the immune system response to an antigen

◀ **Figure 3.** A ureteroneocystostomy

explore the increasingly realistic possibility of a successful renal transplant. After graduating from Harvard Medical School in 1943, he trained in plastic surgery through the US Army at Valley Forge General Hospital, where he gained extensive experience with skin autographs and allografts (7). Given this background, he identified through his training the potential to cross-apply ongoing research in skin grafts between identical twins with surgical attempts at human renal transplants.

Revival of Interest

At the Brigham Hospital, encouraged by success in the canine model, Drs. John Merrill and David Hume had begun experimenting with cadaveric donor kidneys. Between 1951 and 1952, the two conducted nine such operations, whereby the cadaveric kidneys were grafted into the recipients' femoral vessels (8, 9). However, despite technical achievement in four of the surgeries, the most successful host died within six months of the transplant due to insufficient immunosuppression to

allow the transplanted organ to survive. Drs. Merrill and Hume attempted to use corticosteroids as post-operative treatment to decrease inflammation and downregulate the immune response following surgery, but supplies lasted for only a few days (9).

Meanwhile, Dr. Murray had witnessed the outcomes of skin allografts, which rarely survived permanently, but exhibited greater success when grafted between family members, rather than between an unrelated donor and recipient. In 1937, Dr. J.B. Brown at Barnes Hospital in St. Louis took this observation one step further by grafting skin between monozygotic, or identical, twins; as Dr. Brown had hypothesized, this operation resulted in permanent graft survival. Having worked closely with Dr. Brown during his time at VFGH, where Dr. Brown was the

“The significance of a genetic relationship between the donor and host implicated a genetic factor in the immunological response to organ transplantation.”

Chief of Plastic Surgery, Dr. Murray was inspired by his mentor's breakthrough operation. The significance of a genetic relationship between the donor and host implicated a genetic factor in the immunological response to organ transplantation. Two further experiments confirmed this postulation. First, in 1951, Drs. Billingham and Medawar of the University of Birmingham induced acquired immunological tolerance in various mammals, including cows, through a neonatal injection of donor cells into a future allograft host (10). Second, Sir Michael Woodruff of the University of Edinburgh successfully skin grafted between dizygotic, or fraternal, twins who had shared placental blood, which led to a protection against immune response (11). Armed with knowledge of these results, Dr. Murray sought to overcome the immunological barrier in humans that now seemed to be manipulable.

First, however, Dr. Murray had to prove that the transplantation itself of a kidney would not be fatal to the recipient. An autograft, the transfer of a patient's own tissue or organ to another part of his body, would function as a negative control. After repeated experiments in the canine model, at Brigham Hospital, Dr. Murray mastered the technique of grafting the kidney into the lower abdomen, internally connecting the donor kidney blood vessels to those of the recipient's abdomen. Also, a ureteroneocystostomy, by which he placed the upper end of the ureter into the bladder, enabled urine drainage (11). To date, this technique is

used in standard renal transplants, and these kidneys were shown to function completely normally up to two years after surgery (12).

The Case of Richard Herrick

Thus, in 1954, when Dr. Murray was offered the chance to operate on a patient diagnosed with critical renal failure who had a healthy identical twin brother, he leapt at the opportunity. Under the leadership of Dr. Merrill, who was Head of Nephrology at the time, the Brigham Hospital renal transplant team accepted the patient, Richard Herrick, referred by Dr. Donald Miller of the U.S. Public Health Service. Dr. Miller had heard about the Brigham team's ongoing research in the field and recommended to Richard's twin, Ronald, to seriously consider donating his kidney to save his brother's life. Prior to renal transplantation, genetic compatibility was first established by a reciprocal skin graft, which confirmed a genetic match after four weeks without rejection (13).

The final hurdle, then, was the ethical problem of asking a perfectly healthy person to willingly give up an organ for another's survival. Issues arose as to whether the surgeons would be violating their Hippocratic oath to "do no harm" to a patient by excising an organ without conferring any medical benefit to the donor. Ultimately, the operation was justified by the benefits for his twin brother. Still, Ronald faced an ostensibly burdensome decision:

"When it became clear that Richard would die without one of my kidneys, I did some serious soul-searching. I mean, here I was, 23 years old, young and healthy, and they were going to cut me open and take out one of my organs. It was shocking even to consider the idea. I felt a real conflict of emotions. Of course I wanted to help

my brother, but the only operation I'd ever had before was an appendectomy, and I hadn't much liked that" (13).

Dr. Murray and his surgical team took care to avoid pressuring the Herricks to make a decision and instead counseled the brothers to ask as many questions as they felt necessary. Insurance companies assured them that there was no decreased life expectancy associated with

"Dr. Murray proved that a transplantation did not need to occur between genetically identical twins and that the key to a successful transplant was indeed immunosuppression."

only one kidney and chances for disease affecting the remaining kidney remained unchanged. Finally, the Herricks decided to proceed with the surgery; Dr. J. Hartwell Harrison was charged with the removal of Ronald's kidney while Dr. Murray performed the transplant itself (13).

ionizing radiation and cytotoxic drugs like azathioprine to prevent immune cell proliferation (13). After the operation, Richard's new kidney immediately functioned properly, nearly restoring his renal health. He lived for eight years after the operation until renal failure destroyed his new kidney as well (13). In 1956, Dr. Murray repeated the procedure, transplanting a kidney between female twins; the recipient gave birth to a healthy child two years after the surgery and lived through the 1990s, confirming the reproducibility of the experiment. The immense success of this operation not only proved the viability of life-saving organ transplantation but also encouraged further laboratory research into overcoming the immunological barrier.

Beyond the Operation

Dr. Murray himself pursued a means of immune suppression through



▲ Figure 4. Brothers Ronald Herrick (left) and Richard Herrick (right)

Based on the clinical and lab research until this point, Dr. Murray realized the primary concerns were to first surgically insert the kidney and induce function, and then to suppress the immune reaction. Having perfected his technique for the first task, Dr. Murray turned to

laboratory experiments on murine and canine models as well as clinical trials with skin allografts. Different methods he tested included immunoparalysis by repeated grafts, inducing tolerogenicity by exposing the host to donor antigen before operation, and drugs like

toluene (11). Ultimately, though, Dr. Murray pursued what he thought to be the most promising approach: total body X-ray treatment coupled with marrow infusion, first tested on mice and rabbits, then with skin allografts. However, only one out of the twelve patients on whom Dr. Murray used this technique lived beyond three months post-operation. In 1959, this particular patient had received a kidney from his fraternal twin after being exposed to a non-lethal dose of total body X-ray; after the surgery, he led a fully normal life, passing away twenty-five years later due to cardiac disease (11). Thus, Dr. Murray proved that a transplantation did not need to occur between genetically identical twins and that the key to a successful transplant was indeed immunosuppression, though protocol optimization was still on the horizon.

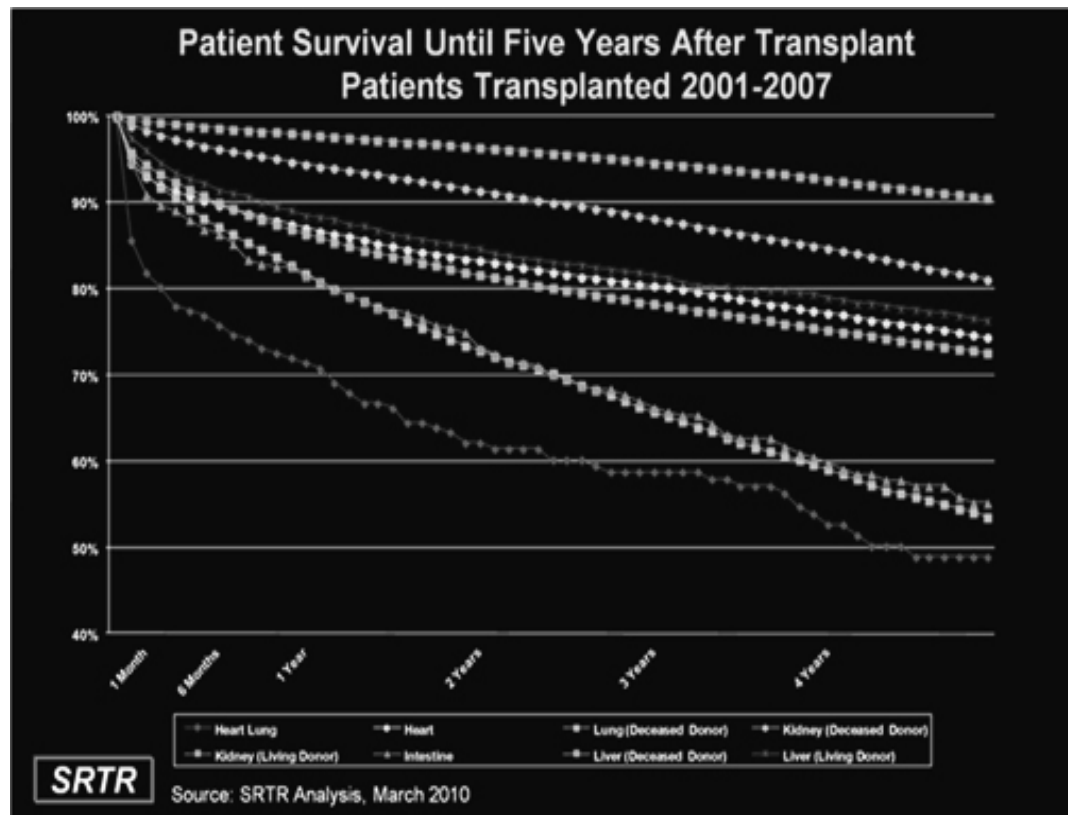
Since the X-ray and marrow infusion approach exhibited a very low success rate, the next largest advancement was the introduction of immunosuppressive drugs in 1959 (11). Using the anti-metabolite 6-Mercaptopurine,

Drs. Robert Schwartz and William Dameshek of the New England Center Hospital inhibited rabbits from producing antigens against human serum albumin, and this tolerance endured even beyond the period of drug treatment. By 1961, a more therapeutically effective drug, known as azathioprine, was discovered and used for twenty years after its introduction. Soon after, cadaveric allografts were used, and by 1965, one-year survival rates for hosts receiving kidneys from living related donors were near 80 percent. The same principles that drove Dr. Murray's experiments encouraged other physicians to expand transplantation attempts to other organs like the liver, pancreas, and heart. In 2010, around 17,000 kidney transplants were performed in the U.S. From 2001 to 2007, over 90 percent of living donor kidney recipients lived at least four years after their operation (Figure 5).

The success of Murray's experiments certainly were not limited to renal transplantation; excitement in the field of organ transplantation quickly spread,

especially among surgeons interested in cardiac transplants. If a kidney could be successfully rescued, then what of the heart—an ostensibly more vital organ? In 1957, surgeons at the University of Mississippi developed a method of such transplantation that involved the replacement of the heart and one lung (15). Using this technique, twelve transplant recipients were able to survive for 7.5 hours after surgery; however, the technique was overly complicated, requiring the surgeons to connect the pulmonary veins with the left atrium. Determined to simplify the surgery while achieving a better success rate, Dr. Norman Shumway of Stanford University experimented in canine models with orthotopic homotransplants combined with oxygenators (15). This technique, adapted from that of the British surgeons Dr. Cass and Dr. Brock, left the left and right atria partially intact. Altogether, Dr. Shumway did see an improvement in success rates: five of the eight dogs survived between six to 21 days after surgery. To date, Shumway's method is used in cardiac transplants (15).

To prolong post-operative life, Dr. Reemstma of Tulane University used methotrexate as a chemical form of immunosuppression, encouraged by the successful use of such treatments in renal transplants (15). When this drug was used in heterotopic canine transplants, rejection was delayed up to 42 days. Using this knowledge, in 1967, Dr. Christiaan Barnard famously performed the first successful human heart transplant in Cape Town, South Africa, with a cocktail of local irradiation, azathioprine, prednisone, and actinomycin C as immunosuppressants (15). From that



▲ Figure 5. Five-year survival rates for heart, lung, or kidney recipients from 2001-2007



▲ **Figure 6.** Dr. Norman Shumway

point on, multiple surgeons repeatedly improved surgical techniques, culminating in the Shumway team's development of a percutaneous transvenous endomyocardial biopsy. This method enabled them to obtain a small tissue sample from the right ventricle via catheter to determine the chances of rejection. By 1974, Stanford had performed 59 human heart transplants, with a survival rate of 43 percent after one year (15).

The final cornerstone in cardiac transplant was not a surgical technique; rather, it was the use of cyclosporine A as a superior immunosuppressive agent. Identified as an immunosuppressant by Swiss Dr. Jean-François Borel in 1967, the metabolite was found to be not only the most effective immunosuppressant in porcine cardiac allografts but also non-toxic (15). With the publication of these findings, Shumway used cyclosporine A in three different dosages in 1980, increasing the one-year survival rate to 83 percent by 1985 (15).

The Future of Organ Transplantation

The perseverance of transplant pio-

neers such as Dr. Murray has revolutionized modern medicine. Organ transplantation today is a viable and valuable therapeutic intervention. There remain, however, major obstacles to be overcome from medical, ethical, and policy perspectives. One major debate surrounds whether or not governments should incentivize organ donation. A successful transplant does indeed ensure a longer, healthier life for the donor, and due to other medical advances that allow patients to live longer with chronic diseases, demand for these organs is ever-growing. This supply-demand mismatch creates a long waiting list, one from which most patients do not live to be removed. Countries like Iran have resolved this issue by creating a national program to incentivize organ donation, particularly by providing health care for living donors (16). However, in the U.S., some scholars fear that putting a financial incentive on organ donation would systematically target the poor and lead to the commodification of human beings (17). Other ethical debates surrounding transplantation focus on how far scientific progress should be translated clinically. The debate continues, for example, regarding whether facial transplantation, as recently accomplished in France and Brigham and Women's Hospital (18), is a justifiable procedure.

Transplantation, pioneered and revolutionized by Dr. Murray at the Harvard

"The perseverance of...Dr. Murray has revolutionized modern medicine."

hospitals, has saved the lives of countless around the world and has improved the lives of millions more. However, the impact of Dr. Murray's experiments was not simply to develop a standard for transplants but also to enhance understanding of the immune system in the context of the whole human body. As evidenced by the work of Drs. Barnard and Shumway, other fields of medicine expanded consequently, including pharmacology. Cyclosporine A is now used

to both suppress the immune response in cardiac transplants and attenuate myocardial hypertrophy. Like all fields of medicine, transplantation surgery will continue to move forward in the years to come, as knowledge of basic science and the restructuring of the healthcare system open treatment options for a larger number of patients. **H**

—*Roxanna Haghighat '15 is a prospective Molecular and Cellular Biology concentrator in Lionel Hall.*

References

1. "Tissue Transplant History" New York Organ Donor Network <<http://www.donatelifeny.org/all-about-transplantation/tissue-transplant-history>> (2011).
2. Edgar, P., Bullock, R., Bonner, S. (2004). Management of the potential heart-beating organ donor. *Continuing Education in Anaesthesia, Critical Care, and Pain* 4(3): 86-90.
3. Simmons, J. "Alexis Carrel." *Doctors and Discoveries: Lives that Created Today's Medicine*. Boston: Houghton Mifflin, 2002. 199-203.
4. "Physiology or Medicine 1990 - Press Release" Nobelprize.org <http://www.nobelprize.org/nobel_prizes/medicine/laureates/1990/press.html> (1990).
5. "Jean Dausset - Biography" Nobelprize.org <http://www.nobelprize.org/nobel_prizes/medicine/laureates/1980/dausset-bio.html> (2005).
6. Murray, J.E. "Nobel Prize Lecture: The First Successful Transplants in Man" Stanford Program in History and Philosophy of Science and Technology <<http://www.stanford.edu/dept/HPS/transplant/html/murray.html>> (2011).
7. "Joseph E. Murray - Autobiography" Nobelprize.org <http://www.nobelprize.org/nobel_prizes/medicine/laureates/1990/murray-autobio.html> (1990).
8. "Joseph E. Murray Biography" faqs.org <<http://www.faqs.org/health/bios/70/Joseph-E-Murray.html>> (2011).
9. "About Dr. Hume" United Network for Organ Sharing <http://www.unos.org/donation/index.php?topic=dr_hume> (2011).
10. Billingham, R.E., Medawar, P.B. (1951). The technique of free skin grafting in mammals. *J. Exp. Biol.* 28: 385-402.
11. "Joseph E. Murray - Nobel Lecture" Nobelprize.org <http://www.nobelprize.org/nobel_prizes/medicine/laureates/1990/murray-lecture.html> (1990).
12. Murray, J.E., Lang, S., Miller, B.J., Dammin, G.J. (1956). Prolonged Functional Survival of Renal Autografts in the Dog. *SGO* 103: 15.
13. Murray, J.E. "Richard and Ronald Herrick." *Surgery of the Soul: Reflections on a Curious Career*. Science History Pubns, 2004. 74-76.
14. "Fast Facts" ustransplant.org <<http://www.ustransplant.org/fastfacts.aspx>> (2011).
15. DiBardino, D.J. (1999) The History and Development of Cardiac Transplantation. *Texas Heart Institute Journal* 26(3): 198-205.
16. Ghods, A.J., Shekoufeh, S. (2006). Iranian Model of Paid and Regulated Living-Unrelated Kidney Donation. *CJASN* 1(6): 1137-1138.
17. Scheper-Hughes, N. (2004) Parts unknown: Undercover ethnography of the organs-trafficking underworld. *Ethnography* 5(1): 29-73.
18. Powell, A. (2009) "Brigham face transplant recipient goes home" *Harvard Gazette* <<http://news.harvard.edu/gazette/story/2009/05/brigham-face-transplant-recipient-goes-home/>>.