History of Organ Transplantation

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The Beginning

On December 23, 1954, two twin brothers were soon to become an integral part of surgical history. Richard and Ronald Herrick were 23-year-old identical twins; however, Richard was dying of chronic nephritis. Ronald was unaware his selfless nature would eventually lead to saving countless lives; his only concern was to save his brother's life. Ronald agreed to donate a kidney to Richard immediately. This transplant, which took five and a half hours, kept Richard alive for eight more years and ultimately led to thousands of kidney transplants and eventual transplants of other organs. Dr. Joseph Murray, the lead surgeon in the transplant at Peter Bent Brigham Hospital in Boston, won the Nobel Prize in 1990 after he discovered that identical twins were ideal candidates for surgery because the transplant ultimately lacked immune problems.

December 1954 - Brigham Transplant Team with Ronald and Richard Herrick

Organ transplantation has been an intriguing topic for hundreds of years. Stories exist of the Chinese Physician Pien Chi'ao who reportedly exchanged hearts between two men: one man had a strong spirit but weak will and the other had a weak spirit but strong will. This alleged transplantation was necessary to create balance among the two men. Another story of Roman Catholic history reports the third-century saints Damian and Cosmas replaced a

gangrenous leg of the Roman deacon, Justinian, with the leg of a recently decreased Ethiopian man.

Saints Cosmas and Damian performing a leg transplant ca 1495

Although these historical accounts of transplantation are most likely fictional, it inevitably piqued the curiosity of many future physicians in attempts to save patient's lives.

Skin and Blood

In the 18th century, Karl Thiersch, a German surgeon, realized skin grafts did not require subcutaneous tissue and succeeded to prove that transplantation from animal to human was not possible without transplant rejection due to incompatibility between the tissues. Thiersch introduced epidermal skin grafting called the "Thiersch graft." This specific grafting method consisted of using only the epidermis and a portion of the dermis. The epithelium is split into thin strips and then implanted onto granulating tissue. This was a great advance in skin transplantation and is still used today.

THE THIERSCH GRAFT. ITS PREPARATIONS AND USES.

FIG. 1.

(*a*) The upper arm properly draped in preparation for the cutting of a graft.

(*b*) The arm supported on the surgeon's knee.
The wood slip and knife in position for cutting the graft.

(*c*) The thigh suitably draped and placed in correct position for graft cutting. The wood slip and knife are in position for cutting from the broadest skin surface available.

(*d*) Wood slip and knife in position for graft cutting in the proximo-distal direction recommended.

Thiersch Graft – mesh graft still used today

In addition to skin grafts, blood transplantation was gaining interest in the 18th century. English gynecologist, James Blundell was the first doctor who created a machine specifically for blood transplantation. He found success in a few patients who experienced excessive hemorrhaging. Although the immediate success gained much optimism, post-transfusion reactions proved a great feat to overcome. In 1900, Paul Ehrlich discovered erythrocytes in blood transfusions that could potentially create hemolytic antibodies. Karl Landsteiner added more explanation to Ehrlich's discovery when he described these antibodies as anti E and anti B and found they would bind on the erythrocytes of graft recipients.

In the 20th century, Alexis Carrel experimented, primarily with dogs, and found a way to effectively anastomose blood vessels. However, this discovery did not successfully bypass the rejection of grafts and transfusions caused by antibodies. Total body irradiation was found to suppress the immune system enough to maintain the transplantation; however the irradiation also produced profound bone marrow aplasia, which resulted in patients' deaths due to

infections. In the 1960s, it was determined that total body irradiation was not the best solution for maintaining the transplant.

Experimenting with Other Organs

The limited success of renal transplantation stimulated the interest in many surgeons to begin experimenting with transplantation of other organs. On June 11, 1963 at the University of Mississippi Medical Center, a man with nonresectable left lung cancer and secondary obstructive atelectasis and pneumonitis agreed to receive a lung transplant as his last resort. Another man had been admitted to the hospital and died shortly after admission due to a myocardial infarction. His family agreed to donate his lungs to the other dying man. A left posterolateral thoracotomy was performed and the left lung was excised after dividing the main pulmonary artery, the left atrial cuff, and the left main bronchus. Drs. James Hardy and Watts Webb quickly anastomosed the superior and inferior pulmonary veins and pulmonary artery and the arterial oxygen increased immediately. Although this patient seemed to have no rejection of the transplanted lung, he died 18 days after the operation due to progressive renal failure and postoperative ileus. At autopsy, it was found that all the vascular and bronchial anastomoses were intact.

Shakespeare wrote, “liver, brain and heart these sovereign thrones.” Because the liver was known as the organ of life (derived from the word “to live”), it was obvious that a patient with a liver dysfunction would ultimately need a new, healthy liver, which could only be done via transplantation. Ten years after the first successful kidney transplant, the first liver transplant was performed by Dr. Thomas Starzl in Denver, CO on March 1, 1963. This liver was donated by a child who had died of a brain tumor and received by a 3-year-old with biliary atresia. The 3-year-old survived only five hours after the transplantation, dying from complications of coagulation and hemostasis during the operation. Although this transplant was unsuccessful,

Dr. Starzl performed a second liver transplant on May 5, 1963; this patient died 17 days later from a pulmonary embolism, but with a healthy liver. Dr. Starzl continued to perform liver transplants in hopes that a long-term success was on the horizon. In 1967, this first long-term liver transplant success was achieved when a patient survived 1 year post transplantation; unfortunately, this patient died due to a recurrence of liver cancer.

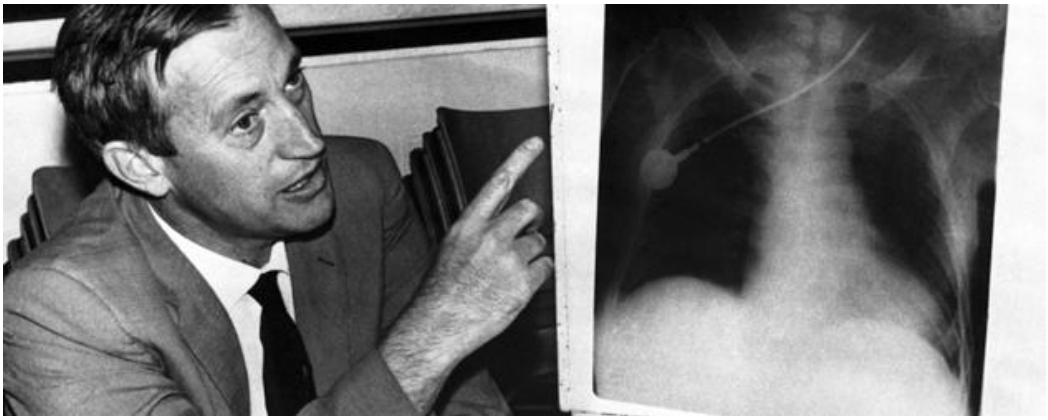
Dr. Starzl and his nurse during an experimental liver transplant, published in LIFE magazine

The first human pancreas transplant was performed by Dr. Kelly, Dr. Lillehei, and Dr. Merkel at Minnesota State University in 1966. The team transplanted a duct-ligated segmental pancreas graft (along with a kidney) from a cadaveric donor. The pancreas segment, which included both the body and the tail, was transplanted extraperitoneally to the left iliac fossa. The great celiac axis was anastomosed to the left common iliac artery. The great splenic vein was attached to its junction with the superior mesenteric and portal vein, which were then anastomosed to the recipient's iliac vein with ligation of the intervening segment. This process converted the donor venous conduit into a bypass graft, which was a procedure devised by Dr. Fred Merkel during his experiments with dogs. The transplant was successful for 6 days, meaning the patient needed no insulin whatsoever. However, the patient soon developed a pancreatic fistula which developed into pancreatitis. This complication resulted in the necessity

of progressively increasing doses of insulin. The pancreatic graft and kidney were removed soon after, but the patient died from a pulmonary embolism 13 days after the removal.

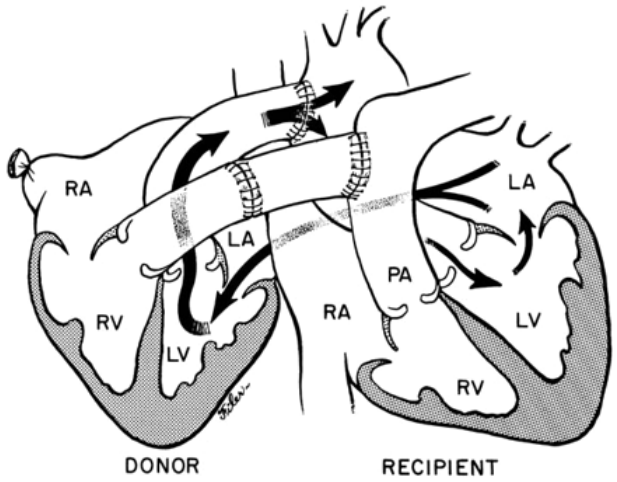
On New Year's Eve of 1966, Dr. Lillehei took on the role as lead surgeon for another pancreatic graft transplant. Dr. Lillehei transplanted a donor's whole pancreas with attached duodenum into a 32-year-old recipient. These were transplanted extraperitoneally to the left iliac fossa. The donor's celiac axis and superior mesenteric artery on a small portion of the aorta were anastomosed to the left common iliac artery. The portal vein was anastomosed to the left common iliac vein. The proximal duodenal end was closed and the distal end, including the first portion of the jejunum, was done as a duodenostomy-jejunostomy cutaneous graft. Unfortunately, this patient experienced post-transplantation rejection of the organs, which affected the duodenum by creating erosions and bleeding throughout. The patient died 4.5 months later from sepsis.

On December 3, 1967, Dr. Christian Bernard performed the first successful heart transplant on a 53-year-old man, Lewis Washkansky, at Groote Schuur Hospital in South Africa. Mr. Washkansky was suffering from diabetes and incurable heart disease and received the heart from Denis Darvall, a 25-year-old bank clerk who had died in a motor vehicle accident. Because Washkansky was given immunosuppressive drugs, his body did not reject the heart transplant; however he contracted pneumonia and died 18 days post transplantation.



Dr. Bernard displaying an X-ray of Louis Washkansky's chest taken during the first heart transplant.

Dr. Bernard was determined to find a transplant procedure that would truly extend a patient's life. In 1974, Dr. Bernard performed the first heterotopic, or "piggyback," heart transplant. During this procedure, the heart of the patient was not removed before implanting the donor heart; instead, the donor heart was positioned so the chambers and blood vessels of both hearts could be connected, essentially forming a "double heart." The two left atria were situated so they could be merged into one large atrium.



A schematic drawing of a heterotopic heart transplant

This type of transplantation is best for patients who have donor hearts too small for their body and would not be able to function alone, if the donor has a weak heart, or if the recipient suffers from pulmonary hypertension. The heterotopic procedure would potentially allow the recipient heart to recover and additionally allow the patient to retain their original heart if the donor heart were rejected.

The Dilemma

Hugo from Bologna (1547-1599) described in his book that transplantation of xenografts from one species to another was not possible. He went on to say that transplantation from human to human or animal to human was also impossible due to the different immunological constituents. Based on the early stories of organ transplantation, one can clearly see that

incompatibility between the donor and the recipient led to major failures in transplant history. Rejection is described as damage to the donated organ by the recipient's immune system. Three types of rejection occur: hyperacute, acute, and chronic rejection. Hyperacute rejection occurs within minutes and is a complement-mediated response. Acute rejection normally occurs 7 days post-transplantation, but can occur months to years after the transplant. Acute rejection is caused by a mismatched HLA, so only those who are identical twins will not experience acute rejection. The kidneys and the liver are the most vascularized organs and are often the first organs to undergo acute rejection. Chronic rejection, on the other hand, is a long-term loss of function of the organs, most often associated with fibrosis of the internal blood vessels of the donated organ. Organ rejection has been noted throughout the years of experimental transplantation and surgeons worked diligently to overcome this devastating setback.

The Revolution

As pioneer transplant surgeons recognized the problem of rejection, they began using immunosuppressive agents in an attempt to maintain the transplant longer. The first step at suppressing the immune system came with full body irradiation. Although it showed some promise, it often caused bone marrow aplasia and resulted in a high mortality rate among transplant patients.

To eliminate the high bone marrow aplasia of irradiation, surgeons began using azathioprine. This drug had very low efficacy and high myelotoxicity in the transplant patient. Cortisone was found to optimize the benefits of azathioprine while reducing its toxicity and was often used in conjunction with azathioprine. This combination was used widely in early transplantation but, due to its low efficacy, it was not particularly successful in saving the transplanted organ from rejection.

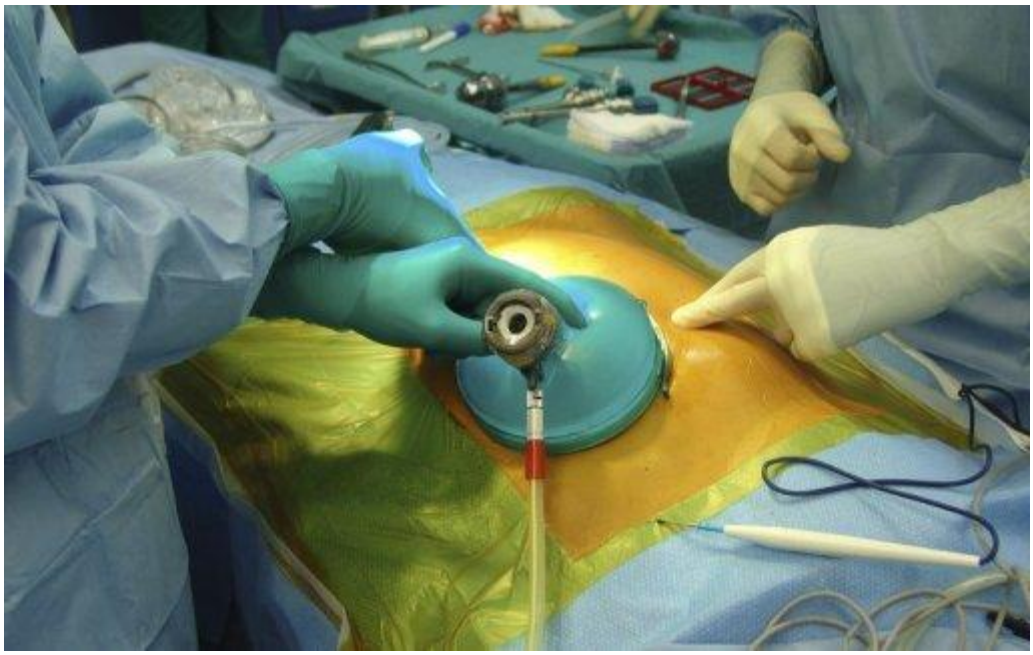
The discovery of cyclosporine in the late 1970s made organ transplantations a true life-saving medical advancement. Cyclosporine is a peptide antibiotic that acts at an early stage in the antigen-receptor induced differentiation of T cells. By binding to calcineurin within the T-cell, it prevents the production of the transcription factor, NF-AT, which is necessary for the activation of T cells. It is essential to monitor the patient's blood concentration of cyclosporine to adjust dosages and ensure adequate immunosuppression and minimize its toxicity. In addition to suppressing the immune system, cyclosporine interacts with many drugs due to its metabolism into more than 25 different metabolites within the cytochrome P450 system.

Tacrolimus is an immunosuppressant macrolide antibiotic that is not structurally related to cyclosporine, but does have a similar mechanism of action. Tacrolimus also inhibits the calcineurin pathway, thereby preventing the production of NF-AT and blocking T-cell activation. Unlike cyclosporine, tacrolimus is 10-100 times more potent in inhibiting the immune response and is now considered a standard prophylactic agent for graft-versus-host disease. Tacrolimus has a narrower therapeutic range and more variable pharmacokinetics than cyclosporine. Like cyclosporine, it also requires therapeutic monitoring. Postoperative ileus and decreased intestinal permeability are common side effects.

With the ability to suppress the immune system, transplant rejection rates have fallen drastically. Prior to the use of cyclosporine, one-year transplant survival rates were approximately 70% for kidneys, 25% for livers, and 58% for hearts. After the millennium, with the widespread use of cyclosporine as an immunosuppressant, one-year transplant survival rates have increased to 90% for kidneys, 80% for livers, and 84% for hearts. In general, for HLA matched living donor kidney transplants, there is a 50% chance of attaining approximately 24 years of function, which is three times longer than the first kidney transplant performed between identical twins Richard and Ronald Herrick.

The Future

The first minimally invasive pancreatic transplant with robotic assistance was performed on September 27, 2010 in Italy. Pancreas transplantation is the only established treatment for long-term normoglycemia in Type I insulin-dependent diabetics. The patient was a 43-yeard old woman who has suffered from type 1 diabetes for over 19 years. The procedure consisted of creating three small holes and an incision of 7 cm and was similar to that of laparoscopic surgery already being performed worldwide.



First minimally invasive pancreas transplant with robotic assistance from the da Vinci surgical system

Throughout the years many surgeons have tried and failed. Despite the failures, these surgeons never gave up on the goal of transplanting a healthy organ into an individual who would have likely died from their own organ failure. With the improvement of transplant procedures, the discovery of immunosuppressant drugs, and, most importantly, the perseverance of many surgeons, organ transplantation has been and will continue to be a life-saving procedure for people from all walks of life. As Christian Bernard said, “It is infinitely better to transplant a heart than to bury it so it can be devoured by worms.”

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