Abstract

Developments in transplantation have progressed dramatically over the past century. Current research is underway to optimize immune modulation, genetically engineering animals for xenografting, and breakthroughs are occurring in regenerative medicine. However, pioneering live-donor transplantation has transformed transplantation in the organ shortage, and these contribute an increased proportion of transplanted organs. Live-donor transplantation is associated with better long-term outcomes, and techniques to recover organs have become less invasive. We set out to examine the evolution of transplantation from its historical beginnings to the developments that make it successful today.

Key words: Transplant, Renal, Delayed graft function, Patterns, Outcomes

Article

Beginnings

The first historical mentions of transplantation begin with the tale of Saints Cosmas and Damian of Aleppo (4th Century), who allegedly replaced the gangrenous leg of a patient with that of a cadaver, with the help of angels.1 Centuries later, surgeons, experimenting with transplants, established that autografts were more successful than allografts. It would take years until Medawar and Gibson2 published their findings on “The fate of skin homografts in man,” where they first described the immunologic aspect of transplant rejection. Significant advances have taken place over the past millennium, beginning with skin autografting, from Tagliacozzi’s adoption and development of Susruta’s nasal flap in the 15th century, to Gillies’ revolutionary pedicle flap during WWI.1

Renal transplantation

In 1902, a Viennese Surgeon by the name of Ullmann autografted a dog’s kidney successfully into its neck, where it lasted for 5 days.1 Attempts by other surgeons to apply the idea clinically were unsuccessful. Jaboulay (1906) in Lyon and Ungar in Berlin both attempted xenografts on patients that failed.1 In 1933, Voronoy1 performed the first renal allotransplantation on a human in Kiev.1 However, this also failed with the recipient dying after 2 days. Voronoy pursued allografting unsuccessfully, with 6 failed operations by 1949.

One of Jaboulay’s students, Alexis Carrel,1 was developing new vascular surgical techniques in transplantation. He moved to Chicago, where work in the field had already been established, to further his career. Together with Charles Guthrie, an American surgeon, he developed the “triangulation technique” for anastomosing blood vessels, where by using fine threads, the ends of an artery are joined by a triangular pattern at 3 equidistant circumferential points,3 and the vessel is sealed with a continuous suture. He also experimented with venous grafts, and performed a successful retransplantation of a limb on a 12-year-old boy, whose arm was severed, suggesting that ischemia during organ preservation was possible for up to an hour. Carrel developed a great preference for using fine needles and threads and became a pioneer of microvascular surgery.
The invention of the “Carrel patch,” anastomosing the base of the renal artery with its surrounding segment of aortic root, improved the technique of arterial grafting substantially and made it easier to work with smaller vessels. He also demonstrated the preservation of vascular grafts by refrigeration. He experimented with the thyroid, the heart, as well as his work with kidneys. He was awarded the Nobel Prize in Physiology in 1912; however, he soon found his pioneering progress heavily limited by the ignorance of immune rejection.

**Discovery of immune rejection**

Around the same time, at Oxford University, Peter Medawar and Thomas Gibson were investigating graft failure. Their first finding was that a second graft from a donor was rejected faster than the first. They concluded that this was because of an established immunity after contact with the first graft. Further testing showed that this effect was exaggerated if the recipient was injected beforehand with donor leucocytes.

The first step in immunosuppression came with Billingham and Medawar’s findings that cortisone prolonged graft survival. Medawar soon published his work with Sir Frank Burnet detailing the mechanism of antigen targeting by the immune system. In 1960, they were awarded a Nobel Prize for this. David Hume in Boston took advantage of the discovery of the effects of corticosteroids, using them in a series of 15 transplants. The successful grafts lasted between 37 and 180 days, which was a remarkable achievement at the time.

**Live-donor transplantation**

The first live-donor renal allograft occurred at the Necker Hospital in Paris in 1952, where a mother offered her kidney to save her son, who had lost his only functioning kidney in an accident. The operation, performed by the surgeon Jean Hamburger, was successful, but signs of rejection began to appear 3 weeks later.

In 1954, the first successful renal transplant, effectively an autograft, was performed by Joseph Murray and his team in Boston, between 2 identical twins. Extensive investigations were performed to confirm this, including the experimental transplant of a skin graft to ensure they were identical. The eventual success of this case suggested that if the immune response could be overcome, successful allografting would be possible. Murray’s contributions over the years would see him eventually awarded the Nobel Prize in Medicine in 1990. Further operations were performed; with up-to-8 years posttransplant survival reported.

Research into immunosuppression grew exponentially. Nephrologist John Merrill, who had participated in the first renal transplant of 1954, conducted studies using newly discovered radiation-based immunosuppression and reported success. The serious adverse events and complications prompted a review of this treatment and its use was discontinued.

**Immunosuppression**

The next pivotal stage came in 1959 in Boston with the discovery by Robert Schwartz that rabbits treated with 6-mercaptopurine displayed a durable tolerance to injected human serum albumin. Prof. Sir Roy Calne, then a registrar in England, used this principle in canine renal transplants, demonstrating successful allografting by administering immunosuppressant 6-mercaptopurine. This formed the basis for further research into more potent drugs, such as ciclosporin, discovered in 1976 by Dreyfuss and demonstrated by Calne in 1979 for use in patients. The discovery of FK-506 (tacrolimus) in Japan by Kino and colleagues 8 years later was another breakthrough, particularly because of its reduced adverse event profile vis-à-vis ciclosporin.

**Liver transplantation**

Liver transplantation, technically a great challenge, did not develop substantially until Welch (1955) conducted his experiments on the transplantation of hepatic allografts into dogs without removing their primary functioning liver.

Thomas Starzl, an American surgeon, began research in 1958 on human histocompatibility at Northwestern Laboratories. The first human liver transplant was performed in Colorado by Starzl on a 3-year-old boy who had biliary atresia, and the operation was unsuccessful. He made 2 further attempts, but they both failed. In 1964, he discovered the presence of hepatotrophic factors in canine splanchnic veins, which altered the understanding of successful hepatic allografting.

In 1965, Gaston Cordier in France reported a lack of allograft rejection in some immunologically unsuppressed pigs. This idea of “spontaneous tolerance” was soon confirmed by Calne in
Thus, began a new line of research investigating the basis for this reaction and potential for its clinical application.

Starzl’s first success came in 1967 in an 18-month-old infant with a hepatocellular carcinoma. The infant lived for a year, before dying because of metastases from the original tumor. Between July 1967 and March 1968, Starzl went on to report 4 out of 7 successful transplants in children.

The first European liver transplant was performed in 1968 by Roy Calne, followed by another 3 in this first series. He reported 1 maximum survival of over 4 months.

Starzl went on to work with hepatic xenografts from baboons attempting to address the donor shortage. He performed 2 successful such liver transplants in 1992 and 1993, raising prospects for xenotransplantation.

The creation of University of Wisconsin preservation fluid by Folkert Belzer and colleagues in 1989 made a dramatic difference to organ preparation and extended the cold ischemia time significantly, from approximately 7 hours to approximately 15 hours. The difference in preservation time revolutionized the dynamics and logistics of liver transplantation, as well as improving results.

**Split-liver transplantation**

In 1984, initial experiments on reduced-size liver transplants in children were conducted by Henri Bismuth. The donor liver was reduced to the left lobe alone, and they demonstrated that pediatric liver transplantation was technically feasible.

These findings were extrapolated in Germany by Pichlmayer who performed the first split-liver transplant in 1988, establishing a logical anatomic approach. He divided the liver into 2 segments, with lobes I and IV-VIII (right) for transplant in an adult and the remaining lobes II and III (left) for pediatric use. He divided the vessels so that the common hepatic artery remained with lobes II and III, and the hepatic portal vein remained with the right lobe. The vascular shortage in the right lobe was tackled by preserving the common hepatic artery in the adult recipient and anastomosing it with the (right) hepatic artery of the donor organ. In the left lobe, the recipient caval vein was preserved and anastomosed with the (left) hepatic vein of the donor organ.

The next year, the first series of split liver transplants was reported by Emond and Broelsch, where they challenged the waste of right lobes in pediatric transplants by sharing the liver as did Pichlmayer. They divided 9 livers for implantation into 18 patients, noting an increase in biliary complications (27% compared with 4%), but similar rates of primary nonfunction and arterial thrombosis. The biliary complications were subsequently reduced by improvements in surgical technique. The differences in recipient and graft survival were not significant ($P = .298$ and $P = .126$) suggesting that split-liver donations were a safe way of addressing the shortage of organ availability.

**Live-donor liver transplantation**

The first mention of living-donor liver transplantation was in a letter to The Lancet published a few months later, in August 1989. Silvano Raia, a Brazilian transplant surgeon, reported 2 living-donor transplants performed that year because of the great organ shortage in Brazil. He pioneered a technique comprising the removal of segments II and III from the donor for transplantation in a recipient with a fully removed liver and entirely preserved vena cava. The vessels were anastomosed in a position optimized by the angled placement of the graft, and hemorrhage was controlled by a simple device invented by their team.

Raia’s first such operation took place in December 1988, on a 4.5-year-old girl, whose mother pledged to be the donor because she had matching blood groups. The mother was discharged 4 days after surgery, but the child had hemolysis, and subsequent renal failure because of “hemolytic antibodies inadvertently transfused in... plasma.” She died while on hemodialysis.

The second operation was performed 8 months later on a 19-month-old girl (blood group A) with hepatic fibrosis, and the donor was a middle-aged man with blood group O. As in the previous case, the donor was discharged shortly after the operation. The patient had acute rejection by the fourth postoperative day, which was controlled with monoclonal antibody (OKT-3). By the 26th postoperative day, she was fully recovering. In his article, Raia concluded that living-donor transplantation can be lifesaving in children with terminal liver diseases, and that its viability had been demonstrated successfully.

Christoph Broelsch subsequently published an impressive transplantation series of 20 children, less...
than 2 years of age, who underwent living-related liver transplants from their respective parents, (1 received a graft from her grandmother). Of those 20 children, 3 died. Of the remaining 17, fifteen were at home with the original functional graft 3 to 18 months after surgery. Technical faults in the first 3 lobectomies performed on the donors were identified. The technique was consequently altered to a segmentectomy, which produced no complications in the remaining 17 donors. Complications in the recipients were attributed to vascular thrombosis, and the research team could reduce with technique refinement. The overall success rate was 75%; as with Raia’s cases, the donors returned to normal health without notable complications. Live-related liver transplantation has become increasingly popular and centers have been adopting it worldwide for adults and children to treat chronic liver disease.

In the spring of 1994, Yoshiho Yamaoka and his team at Kyoto University published an extensive report on the first use of a right lobe graft from a living-related donor at their hospital. During their series of living-donor transplantations, the vasculature in the donor mother of a 9-year-old girl with biliary atresia had irregularly small, complex arterial branching to segments II and III, deeming them unviable for grafting. The prospect of right lobe use was quickly discussed and decided upon. It was removed with care to preserve uninterrupted blood supply as well as the Glisson’s sheath. Subsequently, 625 g of liver was removed and stored in University of Wisconsin preservation fluid at 4°C. The recipient had her 700 g liver removed entirely, leaving the afferent vessels and inferior vena cava intact. The graft functioned well, and a minor complication in portal blood flow on the ninth postoperative day was resolved by removing the responsible hematoma. The mother was soon discharged and 29 months later, the recipient was in good health. Researchers concluded that right lobe use may be advantageous in cases where a greater functional hepatic unit is required.

Conclusion

Today in the United Kingdom, the number of living organ donors is on the rise, accounting for half the number of total organ donors. In 2013, the number of kidney transplants from living- and deceased-donors has increased by 6% and 8%, contributing to a reduction of 4% (compared with 2012) in the number of patients waiting for a kidney. The number of liver transplants from deceased donors has increased by 6%, contributing to a reduction of 12% in the number of patients waiting for a liver transplant. Living-donor liver transplants have contributed 4% of total liver transplants, in contrast with 5% the previous year.

Since Starzl’s xenografts in 1993, the world has seen the discovery of human embryonic stem cells (1998), and the successful transplantation of arms (1998) and a full face (2010). In addition, technology has allowed longer preservation of organs and some centers have extended cold ischemia time to over 100 hours. Pancreatic islet cell transplantation has been used experimentally as a potential treatment for type 1 diabetes mellitus since 1990; techniques have been adapted to achieve greater success. Autologous stem cells have been used to seed a deceased-donor tracheal scaffold, which was successfully transplanted into a recipient with end-stage bronchomalacia. These experimental procedures have yet to come into widespread use.

The statistics above illustrate the role of living-donor transplantation in addressing the organ shortage, and while a reduction in waiting list numbers is evident, an increase in the incidence of diseases such obesity and diabetes is likely to contribute to significant future international demand for organs. With stem cell research still in its early stages, live organ donation is a lifeline to thousands of patients awaiting transplantation.

References


