THE ROAD TO ORGAN TRANSPLANTATION - THE HISTORICAL AND FUTURE ASPECTS

Yannicke Sloots[1]

[1]Bachelor's student Biomedical Sciences, Utrecht university, Utrecht, The Netherlands

Insight

The idea of transplantation has been around for a long time and is described in the mythology of civilisations from all over the world [1]. These legends describe organ transplantations performed by healers and gods. Nowadays, organ transplantation procedures are a reality, and surgeons can save lives of patients with incurable diseases. However, the road towards modern transplantation has been a difficult one and is marked by various important discoveries. Among these are surgical techniques to connect vessels, and the discovery of the immune system and its involvement in rejection of donor organs. Moreover, the introduction of immunosuppressant drugs had a major impact on the field of transplantation. This article will introduce you to the researchers, surgeons, and their findings that paved the way for modern-day organ transplantation.

A leg transplant myth

The journey along the landmarks of transplantation starts as early as the third century. The painting 'The miracle of the Black Leg' depicts two saint physicians, Cosmas and Damien, transplanting a cancerous leg with a healthy one (Figure 1). The story tells us that the man dreamed that Cosmas and Damien came, amputated his leg, and replaced it with one from a deceased Ethiopian man from the graveyard [2]. This was the first time a limb transplantation was mentioned in written literature [1].

First steps

The first documentation of transplantation comes from the sixteenth century. The Italian surgeon Gaspare Tagliacozzi performed skin transplantations to replace missing noses and wrote about these procedures in his book [3]. The first major discovery in skin transplantation came from Jacques-Louis Reverdin in 1869. He showed that small, thin grafts of the epidermis could heal [3]. This technique of skin grafting was used in World War I to treat burns [1]. The first organ transplantation occurred in 1883 and was performed by surgeon Emil Kocher. Kocher treated goitre, a swollen thyroid gland, with operations whereby he completely removed the thyroid. However, all the patients developed the same health complaints, a syndrome we now know as hypothyroidism [4]. Kocher wanted to help his patients and tried to reverse the procedure by transplanting the thyroid tissue back into the patients. Since the organ was replaced to try and cure a complex internal disease, this transplantation may count as the first organ transplant ever [4]. This operation by Kocher became the starting point of research into organ replacement. Researchers started with other endocrine glands, such as the pancreas but also focused on other non-endocrine organs like the kidney.

New techniques

The next step in transplantation in humans were kidney transplants with xenografts, or transplants with organs from another species, for example, pig, goat or monkey donors. These happened around 1906. None of these kidneys functioned for more than a few days, and all patients died [3].

Surgical techniques developed by Alexis Carrel were very important from this moment on. He introduced a new technique for blood vessel suturing that made it possible to connect the donor organ to its vessels in the host. Because the technique of Carrel was so refined, he saw that transplantations between individuals from the same species, or allografts, were unsuccessful due to something that could not be solved by surgical techniques [4]. However, he did not know the reason for the failure of allografts [3].

The rejection problem

As Carrel had experienced with his transplantations, rejection of the donor organ was a major problem. Scientists tried to find explanations for this; maybe rejection had to do with differences in nutrients or protein levels in different bodies. Different experiments were carried out to prevent rejection of allogeneic transplants. For example, the organ was conditioned to its new environment by soaking it in the recipient's blood serum [4]. Another strategy was to reduce the biochemical differences between the donor and recipient, whereby the recipient was fed meat from the donor animal or the recipient was injected with blood from the donor. None of these experiments had promising outcomes. However, a strategy that seemed promising was matching donors and recipients by ABO blood groups or by family relationships. This strategy eventually failed because there was not enough information about how these could predict transplant compatibility [4]. It was Georg Schöne, a German surgeon, who introduced the concept of transplantation immunity which explained that the body's immune system was responsible for transplant rejection [4].

Immune system involvement

A finding in line with the idea that rejection resulted from an immune response was that researchers saw that animals battling an infection had better transplantation results [4]. They reasoned that macrophages were 'tied-up' in these hosts and therefore could not help with the rejection of the donor organ. Another discovery in the early 1900s was the second set phenomenon [3]. This phenomenon was found when a patient that rejected skin grafts from a specific donor was again grafted with tissue from the same donor. This time, the graft was rejected faster, a finding they called the "second set response".

The involvement of the immune system suggested that rejection could be prevented by suppression of the immune system in the

Figure 1: *'The miracle of the Black Leg' painted by Matteo di Pacino (around 1370-135). This painting depicts a story from the third century in which the saints Cosmas and Damien perform a leg transplantation.*

recipient [4]. Different experiments were carried out to suppress the recipients' immune response to try and make the allotransplants successful. Anti-antibodies were produced in 1900 for the first time but did not lead to good results and were therefore abandoned in 1905 [4]. James Murphy showed in 1914 that the lymphoid system caused the resistance to tumour allografts [5]. He tried to block the lymphocytes in the host with irradiation, benzol (the first immunosuppressive agent), and spleen removal. Only radiation had an effect [4, 6]. How the lymphocytes were involved in allograft destruction, Murphy could not explain since, at that time, they thought that lymphocytes were fixed cells. Moreover, radiation and the chemical immunosuppressants were too dangerous for clinical use [4].

A lot was already known about transplantation at this time, but the knowledge could not be translated into applicable procedures. Therefore, after World War I, organ transplantation was given up by the majority of scientists [4]. Only a handful of doctors around the world continued to investigate the possibilities around transplantations.

On to the modern area

In 1945, organ transplantation was rediscovered [4]. Peter Medawar worked with plastic surgeon Thomas Gibson during World War II to explore the use of skin allografts for the treatment of burned aviators. Medawar rediscovered that rejection was an immunologic event but could not detect any antibody [3]. At a cocktail party in 1949, a colleague brought him the idea for his next experiments. In these experiments, Medawar carried out skin transplants in twin cattle. It was already known that identical twins accepted skin grafts from each other. Surprisingly, Medawar discovered that non-identical twin cows also accepted their twins' donor skin, even when the cows were of different genders [3, 7]. Medawar and his team concluded that the twin cows did not recognize the twin cells as foreign because of how their immune systems developed [3].

The team tried the same experiment in mice. They took spleen cells from a donor mouse, then injected those cells into mouse foetuses, and thereby induced chimerism [3]. Chimerism means that there are cells or tissues from two individuals present [8]. The adult mice were then transplanted with skin grafts from the same donor mouse, and these were not rejected [3, 9]. Finally, there was proof that a host could accept an allograft, although it could not be applied to humans yet.

The first kidney transplant

We are now in 1950, and the only successful transplants so far are skin grafts. A kidney transplant was next on the agenda since donors could survive with only one kidney. Dr. Vonoroy was the first doctor to transplant a renal allograft in 1933 . The kidney came from a 6 hours old cadaver, and the patient died in less than 22 hours after transplantation. Blood type incompatibility and ischemia damage have probably led to the failure of this case [1].

In 1953, the 22-year-old Richard Herrick suffered from chronic nephritis, at that time a life-threatening disease with no cure. An American doctor, Joseph Murray, was developing his own procedures to perform kidney transplants, and Herrick went to him for help. Herrick had a healthy twin brother, and his condition was so dangerous that he agreed to undergo the experimental procedure to receive a kidney from his twin brother [1]. Murray and his team first tested the match between the brothers by grafting skin to confirm that they were identical. The brothers underwent surgery in 1954 and became the living proof of the first successfully transplanted organ [1]. By transplanting the kidney from an identical twin, Murray could bypass the issue of rejection because their immune systems matched, something that was already known from skin graft experiments in twins. However, the impact of this success was profound, and Richard Herrick lived eight years with his brother's kidney [1, 3]. Since this was the first successful transplantation, some scientists view this as the first transplantation.

Around 1960, scientists realised that it was impossible to perform all transplants with genetically identical or related donors, so another approach was needed for the evasion of rejection [1].

The first strategy to prevent rejection in non-related recipients came from an experiment in mice. Joan Main and Richmond Prehn showed that when they used radiation to weaken the immune system of adult mice, they could induce chimerism by introducing bone marrow cells. These mice accepted skin grafts from the donor from which they also received the bone marrow [3]. Murray translated this approach to human transplantations and irradiated 12 patients that would receive a donor kidney. Two of these patients received donor bone marrow. Unfortunately, 11 out of 12 patients died within a month [10]. The surviving patient had not received bone marrow but lived with his non-identical twin brother's kidney for 20 years. This was the first time the genetic barrier to human kidney transplantation had been disrupted [3].

Between 1960 and 1962, Jean Hamburger and René Küss showed that this approach also worked between nontwin donors and recipients. They treated four patients with irradiation and subsequently performed a transplant in a non related donor and recipient [11]. All four transplantations were successful. After these successes, researchers assumed that chimerism was not needed for successful transplantation [3].

Immune suppressing drugs

In the following years, immunosuppressant drugs were developed to treat patients and prevent rejection. In 1962, Dr. Roy Calne and his team showed that 6-mercaptopurine prolonged survival after renal transplants in 104 dogs [12]. Together with Murray, Calne found that chemical suppressants such as azathioprine, prednisone, and actinomycin C improved short-term outcomes in human patients [13].

Although the progress in the field seemed positive and encouraging, by 1963, it became clear that the outcomes of transplants were not that good at all. Less than 10% of several hundred allograft recipients had survived as long as three months [3]. Of all patients treated with irradiation, only six had achieved 1-year survival. Immunosuppressive drugs did not seem more effective than irradiation [3].

The American researcher Thomas Starzl brought a new insight into the field. He developed a new immunosuppressive protocol that allowed 1-year graft survival in over 70% of the patients [3]. This new protocol also included immunosuppressive drugs prednisone and azathioprine, but administered these in a specific sequence. This completely changed the outlook for renal transplantation [14]. Some patients could even decrease their drug intake without inducing rejection [3]. The protocol of Starzl remained the virtual world standard for almost two decades [3].

Transplantation of other organs and other developments

The early years of transplantation mostly focused on kidneys, but by the late 1960s, heart, liver, and pancreas transplants from deceased donors had been performed successfully [1]. The amount of successful non-renal organ transplantations grows due to immunosuppression by anti-lymphocyte serum and other immunosuppressive drugs such as cyclosporine (found in 1976) and tacrolimus (found in 1989) [3].

In the Netherlands, 1240 organ transplantations were performed in 2021 [15], while the first successful transplantation occurred in 1954, which is not even 70 years ago. Due to the amazing work of scientists, surgeons, and patients, organ transplantation has gone from a myth to reality.

Acknowledgements

RAMS would like to thank Lars Leenders, Radboud University, as well as R. Neijzen, Utrecht University, for reviewing the article.

References

1. Nordham KD, Ninokawa S. The history of organ transplantation. Baylor Univ Med Cent Proc. 2022;35(1):124–8.
2. Hernigou P. Bone transplantation and tissue engineering, part I. Mythology, miracles and fantasy: From Chimera to the Miracle of the Black Leg of Saints Cosmas and Damian and the cock of John Hunter. Int Orthop. 2014;38(12):2631–8.
3. Barker CF, Markmann JF. Historical overview of transplantation. Cold Spring Harb Perspect Med. 2013;3(4):1–18.
4. Schlich T. The origins of organ transplantation. Lancet. 2011;378(9800):1372–3.
5. Murphy JB. Factors of resistance to heteroplastic tissue-grafting: Studies in tissue specificity. III. J Exp Med. 1914;19(5):513–22.
6. Murphy JB. Heteroplastic tissue grafting effected through roentgen-ray lymphoid destruction. J Am Med Assoc. 1914;LXII(19):1459.
7. Anderson D, Billingham RE, Lampkin GH, Medawar PB. The use of skin grafting to distinguish between monozygotic and dizygotic twins in cattle. Heredity (Edinb). 1951;5:379–97.
8. Yunis EJ, Zuniga J, Romero V, Yunis EJ. Chimerism and tetragametic chimerism in humans: Implications in autoimmunity, allorecognition and tolerance. Immunol Res. 2007;38(1–3):213–36.
9. Billingham RE, Brent L, Medawar PB. Actively Acquired Tolerance' of Foreign Cells. Nature. 1953;172:603–6.
10. Murray JE, Merrill JP, Dammin GJ, Dealt JB, Alexandre GW, Harrison JH. Kidney transplantation in modified recipients. Ann Surg. 1962;156:337–55.
11. Kuss R, Legrain M, Mathe G, Nedey R, Camey M. Homologous human kidney transplantation: Experience with six patients. Postgrad Med J. 1962;38(443):528–31.
12. Calne RY, Alexandre GPJ, Murray JE. A study of the effects of drugs in prologing survival of homologous renal transplants in dogs. Ann N Y Acad Sci. 1962;99(3):743–61.
13. Murray JE, Merrill JP, Harrison JH, Wilson RE, Dammin GJ. Prolonged Survival of Human-Kidney Homografts by Immunosuppressive Drug Therapy. N Engl J Med. 1963 Jan 13 268(24):1315–23.
14. Starzl TE, Marchioro TL, Waddell WR. The Reversal of Rejection in Human Renal Homografts With Subsequent Development of Homograft Tolerance. Surg Gynecol Obstet. 1963;117:385–95.
15. Nederlandse Transplantatie Stichting. Jaarcijfers 2021: aantal orgaantransplantaties gestabiliseerd; wachtlijst stijgt [Internet]. [cited 2022 Mar 22]. Available from: https://www.transplantatiestichting.nl/publicaties-en-naslag/nieuws/jaarcijfers-2021-aantal-orgaantransplantaties-gestabiliseerd-wachtlijst-stijgt