Introduction – Historical Perspective

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"She was of divine race, not of men, in the fore part a lion, in the hinder a serpent, and in the middle a goat, breathing forth in terrible manner the force of blazing fire. . . ." This description by Homer of the mythical creature called Chimera is one of the first known bibliographic references supporting the idea of beings made out of several creatures joined together in a single one. The concept of combining parts of different bodies into one functioning entity is a very old one, expressed mainly in the forms of myths and incarnated via fearsome monsters (chimera), seductive legends (mermaids), luring nymphs (sirens), and many more.

This fictional concept started to materialize initially by the work of an Indian surgeon, Sushruta (1000 BC), who developed a technique to reconstruct large nasal defects by skin grafts, a technique still used in modern plastic surgery. Sushruta was the first surgeon ever recorded to perform transplantation with homologue tissue transfer in the form of skin grafts.

Tissue restoration is found again in the literature in 15 A.D. in the form of a miracle. St. Agatha was sentenced to "be bound to a pillar and her breasts be torn off with iron shears." She endured this prolonged and horrific torture, and she was left in a dungeon to die, only to be visited by St. Peter, who restored her breasts.

The first reference to organ transplantation for therapeutic purposes comes from China, where Hua-To (136–208 A.D.) allegedly replaced diseased organs with healthy ones in patients under analgesia. In the year 300 A.D., Cosmas and Damian performed the miracle of grafting a cadaveric limb onto a person with a diseased leg, marking the first reference to cadaveric grafts. In 1200 A.D., St. Anthony of Padua reported grafting the foot of a young man who had deliberately mutilated himself. All these references depict the development of the concept of organ and tissue transplantation and its evolution from myth, legend, and rumor through the centuries.

The voyage from fiction and myth to reality proved to be a long one, as the dark ages cast a thick shadow upon all scientific development. In the 16th century, the Italian surgeon Gasparo Tagliacozi revived the ancient Indian method of nose

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reconstruction and further developed it by using skin grafts from the inner arm in a two-stage reconstruction. The 17th century is marked by the work of John Hunter, an extraordinary experimental surgeon from Scotland who worked with autografts. One of his famous experiments was the autotransplantation of a cock's claw to his comb.

In 1901, Karl Landsteiner, an Austrian physician, described the first three human blood groups, A, B, and O, and 1 year later, Decastrello and Sturli found the fourth blood type, AB. Landsteiner received the Nobel Prize for his work in 1930. By 1907 blood transfusion became safe, as Reuben Ottenberg performed the first blood transfusion using blood typing and cross-matching.

In the beginning of the 20th century, a famous figure of surgery appeared in the literature, named Alexis Carrel. Born in Lyon in 1873 and trained in France, this skilled experimental surgeon wrote in 1906: "The question of the transplantation of organs in man is a very serious one and difficult, for will the transplanted organ remain and function normally for a long period of time? Another difficulty would be that of finding organs suitable for transplantation into man. A process of immunization would no doubt be necessary before the organs of animals would be suitable for transplantation into man. Organs from a person killed by accident would no doubt be suitable." Carrel described a technique of effective vascular terminoterminal anastomosis, resolving some major technical difficulties of organ transplantation such as graft thrombosis, opening thus the gates for the realization of organ grafting.

This technical advance marks the beginning of a new era in transplantation, the era of multidisciplinary medicine. Surgeons soon realized that overcoming technical difficulties of surgical practice was just the beginning of a difficult journey as immunological issues began to emerge. Remarkably also, in 1910 Carrel intuitively described the problem of graft rejection: ". . .the changes undergone by the organ would be due to the influence of the host, that is, biological factors." From there on, biology, medicine and surgery would have to advance side by side in order to achieve the miracle of transplantation in the form we know it today.

In 1914, Murphy observed that rejected organs are infiltrated by lymphocytes, and with subsequent experimental studies he showed that lymphocytopenia inhibits rejection. Murphy was one of the first researchers to implicate the role of cellular immunity in the rejection process.

In the beginning of World War II, a British medical researcher named Peter Medawar, intrigued by the treatment of burned aviators, focused his research on their treatment with skin grafts. Essentially, when comparing the fate of skin graft taken from the patient itself (autograft) or from another person – the donor – (allograft), Medawar clearly identified the phenomenon of rejection and paved the way for a comprehensive approach to transplantation immunity. By extending his curiosity to animal models, Medawar later demonstrated in mice that full acceptance of foreign skin graft (allograft) could be actively induced by neonatal injection of hematopoietic cells from the donor strain. These pioneer works build the fundamental grounds for the concept of self- and non-self immune recognition and subsequently, for the definition of transplantation tolerance. In the same period, Australian Frank Macfarlane Burnet published his conclusions on immune tolerance and rejection. Medawar and Burnet shared the Nobel Prize for their work in 1960.

The foundations of modern immunology having been laid, the necessity of immunosuppression became evident. The first method of immunosuppression was total body irradiation, characterized by Murray as "blunt and unpredictable." In 1962, the discovery of azathioprine by Nobel Prize laureates Gertrude Elion and George Hitchings and then the discovery of cyclosporine 10 years later, in 1972, by the Swiss biochemist Jean-François Borel, marked the beginning of a new saga, that of organ replacement.

The first organ to be successfully transplanted was the kidney. In 1954, Murray successfully performed kidney transplantation between two monozygotic twins with excellent results. In 1958 Murray, in Boston, and Hamburger, in Paris, started performing a series of human kidney transplantations, initially using total body irradiation as immunosuppression and later the available immunosuppressive drugs.

The success of kidney transplantation sparked the hopes of replacing other organs, and in 1966 W.D. Kelly performed the first human, whole-organ pancreatic transplantation for treatment of type 1 diabetes mellitus. However, this important breakthrough was marked initially by poor results, and very few pancreatic transplantations were performed until 1978, when the combination of newer immunosuppressive drugs and innovative surgical methods yielded acceptable results.

The first human lung transplantation was performed by D. Hardy and his colleagues at the University of Mississippi Medical Center in 1963. The 58-year-old patient died 8 days after the operation of renal complications. Seven years later, Belgian doctors of the University of Ghent performed a successful pulmonary transplantation in a patient with end-stage lung disease. Their patient survived for 10 months.

In 1963, Thomas Startzl performed the first orthotopic liver transplantation. Initial results were disappointing, but Startzl's perseverance and extraordinary surgical skills prevailed, and liver transplantation became a reality. In 1967 Christian Barnard performed a cardiac transplantation in a 54-year-old patient. The operation was successful, and the transplanted heart functioned for 18 days, when the patient succumbed to pneumonia.

Although small bowel transplantation was first performed before 1970, the ubiquitous rejection and total graft failure at the time discouraged the surgical community. However, with the cyclosporine revolution the interest in small bowel grafting was revived and along with the modern immunosuppressive agents, the first successful small bowel transplantation with long-term survival was performed in Germany in 1988 with a graft survival of 4 years.

An important date is the year 1967, when Jan van Rood founded Eurotransplant in an effort to coordinate and optimize organ allocation. The model of Eurotransplant is to establish a central registration of patients on waiting lists and then organize transparently the organ allocation according to equitable medical criteria.

Somehow victims of their success, transplant programs rapidly evolved, and new medical and ethical problems emerged, such as organ shortage, the need to define donor legislation, and priority criteria. In 1984, the National Organ Transplant Act in the United Kingdom laid solid foundations in the medico-legal aspect of human transplantation, setting an elaborate frame for further development in this field by

establishing the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Yet, major concerns remain concerning illegal or unethical activities, such as organ trafficking or transplant tourism.

After a long voyage through the centuries and with the contribution of great minds, organ transplantation is now a reality in every day medical practice. In multidisciplinary coordinated efforts, involving surgeons, physicians, anesthesiologists, immunologists, and researchers across the world, many obstacles have been tackled. Later advancements have come from the technical side, such as the development of living donor transplantations, but also from the pharmalogical side, including the discovery of tacrolimus in 1990, daclizumab in 1997, and sirolimus in 1999. Major challenges have still to be faced, notably, the long-term toxicity of immunosuppressive agents and the problem of organ shortage. These are the key points to improve long-term quality of life of transplant recipients but also to reduce the mortality while waiting for transplantation. As a matter of fact, chronic immunosuppression now represents the leading cause of morbidity and mortality after organ transplantation. Many efforts are currently being made to design new therapeutic strategies, aiming at reducing or discontinuing post-transplant immunosuppression, establishing the so-called transplantation tolerance. In parallel, great hopes are also generated by stem cell researchers as an alternative to whole organ transplantation. Scientists at the University of Minnesota managed to create a functioning rat's heart from the animal's stem cells in the beginning of 2008, opening a door to custom organ creation from the recipient's cells, alleviating any need for immunosuppression.

The future of transplantation is colorfully depicted by the quote of Dr. Doris Taylor of the University of Minnesota: "...What we've done, is hopefully open a door to the idea that we can actually begin to build not just pieces of tissue and organs, but build organs...our hope is that if you need it, we can make it."