

ALLOTRANSPLANTATION, FROM DREAM TO REALTY



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In the vegetal world, grafting can be defined as the natural or deliberate fusion of plant parts so that vascular continuity is established between them, and thus the resulting genetically composite organism functions as a single plant. Vegetal grafts have been performed since antiquity, particularly around the Mediterranean Basin. No wonder, the idea of grafting a portion of tissue, an organ or a limb from one individual to another has been a conscious or an unconscious dream for centuries. We are speaking here not only of implanting a foreign body in a living creature, but to graft living material which will be re-vascularized so as to become an integral part of the recipient host.

MYTHS AND MIRACLES

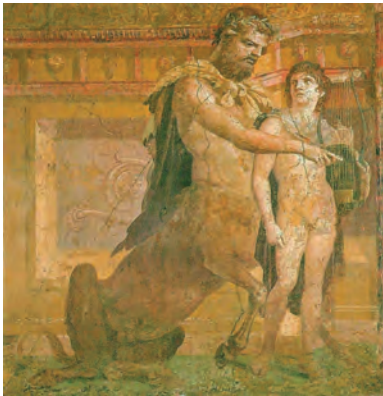


Figure 1 - The centaur Chiron, teaching to the young Achilles (Naples archeological museum)

Hybrid monsters made of different animal or human parts are not rare in the myths of several civilizations. One of the best known in Greek mythology is the Centaur Chiron who had the head and torso of a man and the body of a horse (Fig. 1). Among other qualities, Chiron was celebrated for skillfully applying soothing herbs to wounds and bruises. He was the teacher of Aesculapius, the god of medicine, and is sometimes called the father of surgery.

In the Christian religion, limb transplantation or replantation was considered as miraculous. For example, during the 4th century, in Syria, the twin Greek brothers, Kosmas and Damian, were reputed for their surgical skills, doing operations like amputation of the breast, cure of abdominal fistulas. They were called the *anargyroi* (without money) because they were operating without requesting any fees but required great Christian faith from their patients. Their most known and hallucinating operation was the transplantation of the leg from a recently deceased Moor to replace an amputated limb of a faithful Christian who had a gangrenous infection (Fig. 2). This surgical exploit did not save the two brother surgeons from decapitation by the Roman governor. Later on, they became the patron saints of surgery and since the Middle Ages several associations of surgeons have been called by their name.



Figure 2 - Kosmas and Damian transplanting the leg of a dead Moor, by painter Fernando del Ricon (Prado museum, Madrid)

Other miracles of limb replantation have marked the history of the orthodox and catholic church. St. John of Damascus was a fervid defender of holy icons. Suspecting him of treason, the caliph of Damask ordered as a punishment, to cut off his hand and to put it in the city square.

Later, St. John obtained by praying his cut hand, touched it to his wrist and kneeled in front of the icon of the Virgin Mary. After a long prayer, he felt asleep and dreamed of the Virgin Mary who told him "Your hand is healed because you wrote in defense of God." When St. John awoke, he saw his cured hand and to express his gratitude to the Virgin Mary he ordered to put on the icon a silver copy of the cut hand. That's why the icon is called the Three Handed Virgin. (Fig. 3)



Figure 3 - Three Hands Icon of Virgin Mary

ANECDOTES

During the Renaissance, the possibility of reconstructing a nose with the person's own flesh, as initiated by the Branca family in Catania (Sicily), and later described and illustrated in detail by Gaspare Tagliacozzi (1597), had a large impact in Italy. Moreover, the rumors (fake news of the time!) of transplanted noses from other individuals were frequent and even published by serious doctors. The possibility of re-implanting a nose was even so widespread that the organ was sometimes destroyed so as to be certain that it would not serve as a graft.

Girolamo Sbaraglia (1641-1710), a professor at the University of Bologna, claimed that a patient received the nose of a porter and "that the story finished badly in that the nose fell off when the donor died." This report led famous writers and poets like Samuel Butler¹ or Voltaire to mock and propagate these strange stories. Even in the 19th century, a thriller written by the French author Edmond About "The notary's nose" had immense success. It relates the story of a notary who had lost his nose in a fight and paid a prisoner in order to harvest the skin of his arm to make the reconstruction. The notary's nose fell off, when the donor had his arm amputated after an accident.

FIRST EXPERIMENTS

Abraham Trembley of Geneva (1710 - 1784) is best known for being the first to study freshwater polyps or hydrae and to develop experimental zoology.



Figure 4 - Drawings of Trembley's experiment on hydrae

Trembley's findings were published in a groundbreaking book in 1744, *Mémoires pour servir à l'histoire d'un genre de polypes d'eau douce*. In his experiment, he was not only able to observe the possibility of regeneration of an amputated part of the animals, but also to achieve the fusion of fragments of two different animals, producing for example polyps with 16 limbs instead of 8. (Fig. 4) This was the first allotransplantation in animals duly recorded. (1)

¹So learned Tagliacotius, from The brawny part of porter's bum cut supplemental noses which would last as long as parent breech; but when the date of the nock was out, off dropped the sympathetic snout.

In 1804, the Milanese physiologist, Giuseppe Baronio, published his three experiments of skin autografts in a ram, one of them considered as successful (Fig. 5). In a following experiment, he harvested a piece of skin from the neck of a gravid mare and an equal piece on a cow's neck and cross-grafted the two animals. As we can expect, it was a failure that he attributed to either the motions of the animal's necks or to the "heterogeneous" material. (2)



Figure 5 - Skin grafts on a ram by Baronio

In 1822, the famous Berliner surgeon Dieffenbach wrote his PhD thesis on the subject of grafting but was forced to admit that his attempt to transplant skin ended in total failure. He wrote however: "It would be an interesting and well deserving work to unite, in a small treatise on the transplantation of animal parts, all the observations disseminated in essays on physiology and surgery. We may still hope that at length, correct and repeated observations would probably enable us to penetrate this grand mystery of nature". Paul Bert (1833-1886), a French physiologist, encouraged by Dieffenbach, spent a substantial part of his career studying animal grafts, making a clear distinction between grafts carried out on the same animal, between two animals of the same species, or in animals of two different species, coining the words *autografts*, *homografts* and *heterografts*. In Bert's experience, autografts were the most successful, but he did not rule out the feasibility of other types of grafts, even in humans. He also tried to repeat the experiment of Trembley, by grafting half a body of a soft water hydra to another, but did not succeed. (3)

THE DISCOVERY OF JAUQUES LOUIS REVERDIN (1869)

The communication of the young Swiss doctor at the Imperial Academy of Surgeons in Paris on the 8th of December 1869 has become a landmark in the history of grafting. (4) The purpose of skin grafting for Reverdin (like for Thiersch later on) was to accelerate and enhance wound healing following trauma. But in the years following 1870, several articles reported the development of full thickness skin grafts to correct eyelid ectropions or replace skin defects surgically created on the face. Already in 1884, Emil Bock, an ophthalmologist, had collected more than 200 published articles describing various skin and mucosal grafts. (5)

WHAT ABOUT ALLOGRAFTS AND XENOGRAFTS?

What may seem to us today an imposture is the fact that about half of these reports deal with skin allografts and even xenografts. Reverdin himself stated: "I often took the skin fragments on myself, to graft them on patients who would refuse the operation, thinking that it was painful. In our first grafts, I had taken the tegument on the subject himself, but I soon became assured that the result was the same when transplanting grafts from one subject to another; this fact has been abundantly demonstrated". Even more surprising is the fact that many surgeons, particularly ophthalmologists, claimed to practice successful xenografts, using frog skin for eyelid repairs.

In fact, for decades, most surgeons believed that a skin transplant could be harvested on another person or even on animals. The use of cadavers or amputated limbs as donor sites was common and was almost never questioned. Even during the early 20th century, Alexis Carrel, Nobel Prize winner in 1912 for his research on organ transplantation, claimed that he had grafted successfully skin from a black dog to a white one. How can we explain that most of these researchers never realized that on the long-term all these allografts would fail? Of course, there were some discordant views. In the 16th century, Gaspare Tagliacozzi was already doubtful in this matter and questioned: "Is it possible to take skin from another person, and if this is possible, will it be more successful and advantageous? No: the single character

of each individual speaks against the harvesting on another one. For such is the force and power of individuality." Louis Ollier (1830-1900), the father of bone and periosteal grafts, was against skin allografts but in favor of allografts only for the bones: "one does not fear to inject in the veins of a sick person the blood of another individual. We don't see why a wounded man could not profit from an amputated limb that the amputee would be glad to abandon". Ollier was however totally opposed to bone xenografts. (6)

We are indebted to Erich Lexer who in 1914 put serious doubts on the permanent viability of skin allografts and xenografts. In his publication, he starts by making the difference between the healing of transplanted tissue with revascularization of the cells, the disintegration of the transplanted tissue, with coincident regeneration of the homologous tissue of the recipient, and the healing with complete encapsulation. All types of tissue, such as connective tissue, fascia, tendons, fat, vessels, peritoneum, cartilage, and bone can be made viable in the homologous tissue of the recipient, he wrote; but for skin transplantation, "I am compelled to say that homoplasty does not yield good results. The fortunate healings of transplanted skin by homoplasty reported in the literature are the result of erroneous observations." (7)

From this time on, we see the development of allotransplantation research of a more sophisticated nature with the formulation of several hypotheses on the causes of the failures. The *immune concept* was advanced by several workers like Georg Schöne in 1914, (8) or the *individuality differential* hypothesis by Leo Loeb in 1921. (9) But it was not until 1946 that Medawar reported his experimental work on rabbits, as the result of which the immune theory was clearly established. He postulated that homograft rejection was the end product of an interaction between antigen present in the donor cells and antibody produced by the recipient. (10)

THE MORAL ISSUE OF ALLOTRANSPLANTATION

The fear against allo- or xenotransplantation is that a tissue or an organ of an animal or another individual might modify not only the body of the recipient, but also his identity or even his soul. Around 1670, a certain doctor von Meeckren reported that he repaired the skull of a Russian soldier, killing a dog and using its calvarium to replace the missing part. The patient healed perfectly, but the Church condemned the operation, and the implant had to be removed under the threat of excommunication. Doctor François Rabelais, the famous French writer of the burlesque book *Pantagruel* (1532), even imagined once that a cut off head could be re-implanted and did not hesitate to relate it with several technical details. Epistemon, the patient, regained all his spirits after the operation.



Figure 6 - Portrait of John Locke

A century later, more seriously, the philosopher John Locke (1632-1704) (Fig. 6) in his most comprehensive analysis of *Identity and Diversity* in animals and humans, raises several fundamental questions. After defining what is the Identity of a person, linked to his body and to his soul throughout the elapse of time, Locke brings up the question of what will happen if the brain of a prince is transplanted into a cobbler: "For should the soul of a prince, carrying with it the consciousness of the prince's past life,

enter and inform the body of a cobbler, as soon as deserted by his own soul, every one sees he would be the same person with the prince, accountable only for the prince's actions: but who would say it was the same man? The body too goes to the making of the man, and would, I guess, to everybody determine the man in this case, wherein the soul, with all its princely thoughts about it, would not make another man: but he would be the same cobbler to everyone besides himself."

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MONTANDON CONTINUED

Another issue of moral implication of grafting was raised by the experiment of Trembley in creating a new living body (animal) by joining the two halves of two animals. Creationism was widely held at this time and many people were shocked, because only God could create a new animal. In 1896, HC Wells, famous for his science fiction books, and a strong believer in homo- and hetero-transplantation, seriously frightened the readers of "The Island of Doctor Moreau", by imagining the possibility of "superseding old inherent instincts by new suggestions, grafting upon or replacing the inherited fixed ideas," and creating hybrid monsters.

Since that time, the question of identity and uniqueness of a person in relation to foreign grafts has been much debated by ethicists, psychologists, and immunologists. The French philosopher Jean-Luc Nancy, who underwent himself a cardiac transplant, interviewed a series of patients who had their life saved by liver, kidney, pancreas, lung and heart transplants. His writings explore the subject of "being oneself and another: the paradoxical identity of the receiver. The grafted person must survive, being one and multiple at the same time, and wear in himself a dead living." Multiple philosophical questions are raised: the relation of the biological and the subjective identity, the relation of the subject to his body, the ontological and juridical status of the human body in our society. (11) Facial graft makes no exception to this debate and has already been initiated after the first facial transplant in France. The world's first human head transplant is set to take place soon according to the Italian neurosurgeon Dr. Sergio Canavero. When it does, it will be urgent to answer the interrogation raised by Rabelais, Locke and Nancy.

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CONGRESS PHOTOS

