

Addendum

Composite tissue allotransplantation - Global perspectives

Composite tissue allotransplantation (CTA) adheres to the tried and tested trends of organ transplantation: harvesting from the donor in dead cerebral status, immunological incompatibility between donor and recipient, and life-long immunosuppression of the recipient. The immunology of CTA grafts is complex, making CTA tolerance more difficult to achieve than organ tolerance.

In the early 1950s Harrison *et al.*^[1] and Hamburger *et al.*^[2] performed the first successful kidney transplants, leading to a rapid expansion of the field of solid organ transplantation. This success in solid organ transplantation led a team of surgeons in Ecuador to perform the first cadaveric hand transplant in 1964.^[3] Unfortunately, the immunosuppressive regimen used (azathioprine and hydrocortisone) was insufficient, and the hand got rejected and was subsequently amputated 2 weeks post-transplant.^[4] From solid organ allotransplant to CTA was a long wait. CTA whether hand or face was not a life-saving procedure, requiring life-long anti-rejection treatment with potentially serious side-effects. Hand transplantation and face transplant were, therefore, a controversial concept with ethical, financial, and psychological implications that needed careful consideration and acceptance both from the scientific community as well as the society at large.

One of the first accounts of transplantation dates back to 348 A.D. in which the sainted twins Cosmas and Damien replaced the gangrenous, cancerous leg of a sleeping man with that of a recently deceased Ethiopian Moor.^[5] This important contribution to medicine was immortalised a century later in the famous painting of 'The Legend of the Black Leg' by

Da Varagine in 1270 A.D.^[6] Then in the 16th century in Bologna, Italy, Gaspare Tagliacozzi, of Rhinoplasty fame, reportedly used a flap of tissue transplanted from a slave to reconstruct the severed nose of a man. The story goes that the reconstructed nose survived for 3 years, until its donor died, at which time it rejected.^[7,8] Immunological rejection plagued this science for a very long time till in the early 1950s, the pioneering work of Gibson, Medawar, Billingham and Brent in Britain and Owen in the USA began to probe the causes of rejection and laid the foundation for the field of transplantation immunology as we know it today.

Attempts to obtain an efficient, yet non-toxic immunosuppressive treatment have always been the limiting factor of organ transplantation. Introduced in 1982, cyclosporine dramatically improved the survival rate of patients by preventing graft rejection without undue toxicity. Other immunosuppressive agents introduced in recent years (tacrolimus, mycophenolate mofetil, monoclonal antibodies, antilymphocytic immunoglobulins, etc.) have widened the therapies available to face any situation of rejection and have limited the toxic effects specific to each drug. Tissue transplantation benefited from the progress of immunosuppression, but immunological specificities of composite tissues delayed the development of an efficient yet non-toxic protocol. Unlike solid organ allografts, composite tissue allografts such as a hand or an entire limb, are histologically heterogeneous and are composed of tissues that express varying degrees of antigenicity. Among these tissues are skin and muscle, which are highly antigenic and other immunocompetent

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components such as bone marrow and lymph nodes, which may participate in the immunological reaction.

CTA rapidly progressed in the 1980s with the discovery of cyclosporine. Although, the most success has been achieved with hand transplantation, others have made progress with allografts of trachea, peripheral nerve, flexor tendon apparatus, vascularised knee, larynx, abdominal wall, and most recently, partial face. The world's first partial face allotransplantation occurred in November 2005. Bernard Devauchelle, a Frenchman, Benoit Lengelé, a Belgian plastic surgeon, and Jean-Michel Dubernard in Amiens, France were the first team to conduct a face transplant. Isabelle Dinoire underwent surgery to replace her original face, which had been mauled by her dog. In April of 2006, there was a second performed in China. Complete facial/scalp allotransplantation offers a viable alternative for unfortunate individuals suffering severe facial disfigurement of burns and trauma and is a product of many decades of experimental research. When a face transplant is performed, the recipient does not take on the features of the donor. Only the skin of the face and missing hard tissues are transplanted, with the underlying muscle and remaining bone structure being of the recipient. The resulting face is often described as a "hybrid" between the donor and the recipient, as the new face will not be a perfect match for the old one. This will result in several psychosocial issues.

One of the most exciting applications of vascularised tissue allotransplantation in functional reparative surgery is that of the first larynx allograft performed in January 1998 by M. Strome at the Cleveland Clinic in Ohio, US, in a 40-year-old man, aphonous since the age of 20 after the traumatic avulsion of his larynx.^[9] He received an allograft of the complete pharyngolaryngeal system (larynx, pharynx, 6 laryngeal rings, 2 superior and recurrent laryngeal nerves, superior thyroid arteries, right internal jugular vein and left middle thyroid vein, thyroid and parathyroid glands). After a 10 hours cold ischemia time, the graft was revascularised on the recipient by the right vessels. It was suspended to the hyoid bone superiorly, sutured to the 5th tracheal ring inferiorly and to the oesophagus posteriorly, followed by the anastomosis of the left vessels prior to the 2 laryngeal nerves and right recurrent nerve. The patient received an initial treatment of monoclonal antibodies OKT3, cyclosporine, mycophenolate mofetil, and methylprednisolone, followed by a maintenance therapy of tacrolimus, mycophenolate mofetil and prednisone.

The post-operative phase was turbulent to say the least but at 16 months postoperatively, the various parameters of the voice (tone, quality, intensity, flow, and respiratory coordination) were normal. The patient talked with a perfectly intelligible voice and obtained efficient deglutition after 3 months.

In July 2015 Zion Harvey, a 8 year old boy became the youngest patient to receive a double hand transplant. An active young boy, Zion's hands and feet had to be amputated when he was a toddler after he contracted a serious bacterial infection. However, with the help of prosthetic legs, the schoolboy is able to walk, run and jump like his friends. He had also learned how to write using his forearms and was already able to feed himself and play video games before his transplant at The Children's Hospital of Philadelphia. As he was already taking the anti-rejection drugs for a kidney transplant, he was ideally suited for a double hand transplant. Dr. L Scott Levin, his surgeon described this surgery rightly as "a huge step forward in worldwide transplantation."^[10]

Hand transplants that have been performed in humans since 1998, have proved that the immunological obstacle can be overcome without major difficulties and that the graft eventually shows bone consolidation and tissue healing similar to the patient's own tissues. The surgery was, however, criticised by those who doubted the ability to functionally recover after the operation and opposed the procedure due to the risk of complications. They felt that having hands, or a voice are non-critical to 'life', it seemed unwarranted to subject handicapped but 'healthy' patients to the risk of lethal complication, even a 1% risk. Other progressive minds who considered that the quality of life is an even more important consideration than just 'staying alive', defended hand transplantations performed in a rigorous and scientific environment. The amputation of the first hand transplant in February 2001, 2 years and 4 months after the transplant was done because the patient never submitted himself to the constraints inherent to the intervention (the physical therapy, the therapy observance, the side-effects of the treatment, and the close medical monitoring) not only taught surgeons to choose the patients well but also suggested that reversing the procedure remains a solution to potentially unacceptable complications or even for unsatisfied patients.

The quality of the functional results depends, to a large extent, on the integration of the graft in the body identity

of the transplanted patient, that is, the recognition and the acceptance of the graft as 'self'. Functional magnetic resonance imaging performed on the patient who received a double hand transplant in Lyon in January 2000 showed that the cerebral motor cortex is able to restructure itself to recognise and activate the transplanted hands, even after the long period of sensitive deprivation due to the amputation.^[11] A risk, however, exists that the patient becomes preoccupied with the foreign origin of the graft, which may lead to its 'psychological rejection', as after some cosmetic surgery procedures such as breast augmentation with silicone implants.

Abdominal wall transplantation is a type of composite tissue allograft that can be utilized to reconstitute the abdominal domain of patients undergoing intestinal transplantation.^[12] The first abdominal wall transplant was performed in 1994. The Abdominal Wall Vascularized Composite Allotransplant (AW-VCA) differs from the other VCAs in that it is currently only performed in conjunction with intestinal and/or multivisceral transplantation. In addition, it is the only nonfunctional composite tissue transplant routinely performed. The first successful lower extremity transplant was reported by Zuker *et al.* in 2006^[13] and bilateral transfemoral transplantation was performed in 2012 and one year post operative results were presented by Cavadas *et al.* in 2013.^[14]

The principle of 'like with like' reconstruction, specific to tissue allotransplantation, gives hope to the broadening of the 'field of possibility' in reconstructive surgery to physical handicaps with no current solution. Allotransplantation, however, has many disadvantages:

1. The side-effects of immunosuppression (metabolic disorders, malignancies, infections)
2. The risk of transmitting infection that might elude from current techniques of detection
3. The indispensable matching of donor and recipient under cosmetic criteria (gender, ethnic background, and morphology) is complicated by the current lack of organ and tissue donors in some countries. Organs can come from any source but exposed body parts must have a reasonable aesthetic resemblance with the recipient.
4. The uncertainty over the long-term results: While the functional results of these allografts should improve with time and physical therapy, some immunological phenomenon might curtail these results in the long-term. The functional capacity of kidney and heart

decrease with time, so how a heterogeneous group of tissues will respond is not very clear.

The limited side-effects of the immunosuppressive treatment and the benefits of the transplantation — functional, and more importantly psychological, manifesting from the restoration of body integrity confirm that these operations were reasonable, and even justified. However, CTA should still be regarded as an extreme solution for exceptional indications. Efficacious, safe and ethical clinical tolerance protocols could further improve patient acceptance of composite tissue allografts.

CTA area is among the newest and the most happening arena of reconstructive surgery. The immunology of composite tissue allografts is complex, making tolerance more difficult to achieve than organ tolerance after a kidney or a liver transplant. Any episodes of acute rejection should be prevented for the perfect restoration of function and to minimise the risk of chronic rejection in composite tissue allografts. Efficacious, safe and ethical clinical tolerance protocols could improve patient acceptance of composite tissue allografts by providing an alternative to chronic immunosuppression.

Continued success in clinical CTA over the last few years has convinced the transplant community to shed its skepticism that all attempts at CTA are ambitious and misguided. Meanwhile, this new procedure should not be forbidden nor recommended, but reserved for a few teams that are experienced in both reconstructive and transplantation surgery. Restricted to major handicap conditions and performed under the fundamental guidelines of medical ethics — professional competency, therapeutic objective, and information about the patient — CTA is a rightful expression of reconstructive surgery.

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