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REVIEW

Composite tissue allotransplantation of the hand and face: a new frontier in transplant and reconstructive surgery

Brian Gander,[1] Charles S. Brown,[1] Dalibor Vasilic,[1,2] Allen Furr,[3] Joseph C. Banis Jr,[1] Michael Cunningham,[4] Osborne Wiggins,[5] Claudio Maldonado,[6] Iain Whitaker,[7] Gustavo Perez-Abadia,[6] Johannes M. Frank[8] and John H. Barker[1]

1 Department of Surgery, University of Louisville, Louisville, KY, USA
2 Department of Plastic, Reconstructive and Hand Surgery at the University of Utrecht, Utrecht, The Netherlands
3 Department of Sociology, University of Louisville, Louisville, KY, USA
4 Department of Communication, University of Louisville, Louisville, KY, USA
5 Department of Philosophy, University of Louisville, Louisville, KY, USA
6 Department Physiology and Biophysics, Health Sciences Center, School of Medicine, University of Louisville, Louisville, KY, USA
7 Department of Plastic, Reconstructive and Burns Surgery, The Welsh National Plastic Surgery Unit, The Morriston Hospital, Swansea, UK
8 Department of Trauma Surgery, Johann Wolfgang Goethe University, Frankfurt, Germany

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Correspondence
Dr John H. Barker MD, PhD, Professor of Surgery, Director, Plastic Surgery Research, University of Louisville, 511 South Floyd Street, 320 MDR Building, Louisville, KY 40202, USA. Tel.: +1 502 852 0167; fax: +1 502 852 1256; e-mail: jhbark01@louisville.edu

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Summary

Each year an estimated 7-million people in the USA need composite tissue reconstruction because of surgical excision of tumors, accidents and congenital malformations. Limb amputees alone comprise over 1.2 million of these. This figure is more than double the number of solid organs needed for transplantation. Composite tissue allotransplantation in the form of hand and facial tissue transplantation are now a clinical reality. The discovery, in the late 1990s, that the same immunotherapy used routinely in kidney transplantation was also effective in preventing skin rejection made this possible. While these new treatments seem like major advancements most of the surgical, immunological and ethical methods used are not new at all and have been around and routinely used in clinical practice for some time. In this review of composite tissue allotransplantation, we: (i) outline the limitations of conventional reconstructive methods for treating severe facial disfigurement, (ii) review the history of composite tissue allotransplantation, (iii) discuss the chronological scientific advances that have made it possible, (iv) focus on the two unique clinical scenarios of hand and face transplantation, and (v) reflect on the critical issues that must be addressed as we move this new frontier toward becoming a treatment in mainstream medicine.

Introduction

Each year an estimated 7-million people in the USA need composite tissue reconstruction because of surgical excision of tumors, accidents and congenital malformations [1]. Limb amputees alone comprise over 1.2 million of these. This figure is more than double the number of solid organs needed for transplantation [1]. The concept of composite tissue allotransplantation (CTA) is not new. As far back as the fourth century twin brothers Saints Cosmos and Damian were said to have replaced the diseased limb of a sleeping man with that of a recently deceased moor [2]. Centuries later in 1963, a hand transplant was attempted in Ecuador [3], but was rejected after only 3 weeks [4]. The development of more efficacious immunotherapy in the 1980s moved the possibility of successful CTA closer to reality. The truly modern era of CTA dawned in 1998, when an international team performed a successful hand transplant in Lyon, France. To date, 24 hand transplants and two face transplants have

been performed (Table 1). These breakthroughs have captured the public's imagination, and stimulated a great deal of discussion in the lay and scientific communities.

Historically, transplant and reconstructive surgeons have enjoyed a close relationship having worked hand in hand advancing their respective fields. The publicity and reaction to the recent hand and face transplants are reminiscent of the first cardiac transplant performed in 1967 by Christian Barnard in South Africa. Although the consensus of the medical community at the time was that the world was not ready, this procedure undoubtedly energized many centers throughout the world and accelerated successful outcomes.

In this manuscript we: (i) outline the limitations of conventional reconstructive methods for treating severe facial disfigurement, (ii) review the history of composite tissue allotransplantation, (iii) discuss the chronological scientific advances that have made it possible, (iv) focus on the two unique clinical scenarios of hand and face transplantation, and (v) reflect on the critical issues that must be addressed as we move this new frontier toward becoming a treatment in mainstream medicine.

Limitations of conventional reconstructive surgery

Conventional reconstructive treatments include (i) reattaching amputated body parts using microsurgical techniques, (ii) transferring adjacent or distant autologous tissues to reconstruct tissue defects and (iii) using prosthetic materials to hide or disguise the tissue defect.

Over the years advances in these conventional treatments have greatly improved the surgeon's ability to cover large tissue defects and to a large extent even restore form and function. Of the conventional methods listed above the first provides, by far, the best aesthetic and functional outcomes due to the fact that the defect is reconstructed using the original tissue. However, this option is often not possible because the tissue in question was destroyed beyond use (burns, cancer extirpation) or because the tissue did not exist in the first place (congenital birth defects). While the later two treatments (autologous tissues and prosthetics) do a good job of covering large wounds they are associated with several shortcomings including technical failure, infection, rejection of the prosthetic materials, and poor functional return and cosmesis. In addition conventional treatments often require multiple follow-up revision surgeries and prolonged rehabilitation, which impede patients from returning to work and normal life. All of these factors place a tremendous negative impact on patients who suffer with these deformities, their family upon whom the burden of care and dependency often falls and ultimately our healthcare system and society that must absorb the financial cost of multiple procedures, prolonged hospitalization, and loss of work productivity. Composite tissue allotransplantation (CTA), in the form of hand and face transplantation could eliminate many of these complications and drawbacks and provide superior functional and aesthetic outcomes and in doing so would revolutionize the field of reconstructive surgery [5].

The history of composite tissue allotransplantation

Long before solid organ transplantation was considered, 'The legend of the black leg' (*Leggenda Aurea*) recounted the tale of twin brothers Cosmas and Damian who replaced the diseased leg of a sleeping man with that of a recently deceased Ethiopian Moor in 348 AD [2]. This legend has been immortalized in several paintings by a number of 15th century artists [6]. In the 16th century, in Bologna Italy, Gaspare Tagliacozzi, (1547–1599), considered by many to be the father of modern Plastic Surgery, described transplantation of the nose from a slave to his master. Interestingly, the reported death of the slave 3 years later, corresponded to failure of the transplant [7]. Subsequently, several reports of tissue transplants appeared periodically in the literature. The first substantiated successful allotransplant was that of sheepskin reported by Bunger in 1804 [8]. In the early 1900s Carrel described successful orthotopic hind limb transplants in dogs [9]. Subsequently, Alexis Carrel described connecting an artery from the arm of a father to the leg of his infant son in order to treat intestinal bleeding. Although this experiment was a success, the discovery of anticoagulants soon made such direct transfer unnecessary. For his pioneering efforts, Carrel won the Nobel Prize in 1912 [10]. Around the same time Guthrie described heterotopic allotransplantation of dog heads onto the neck of recipient dogs. Restoration of salivation and eyelid function in the transplanted heads was reported postoperatively [11]. Although these studies laid the foundation for the development of the surgical techniques (microvascular nerve and vessel repair) necessary to transplant tissues and organs, the immunological barriers were yet to be addressed.

The tragedies of war provided the impetus for beginning to study the immunological barriers associated with tissue allotransplantation. A large number of severely burned fighter pilots in the Battle of Britain in World War II were the catalyst for the formation of a burns unit at the Glasgow Royal Infirmary. The appointment of a young Plastic Surgeon, Thomas Gibson and a Zoologist, Peter Medawar allowed several early advances. While caring for these patients Gibson noted that those who received skin grafts transplanted from another individual demonstrated accelerated rejection following a second

Table 1. Hand and face transplant data.

Type of CTA	Date performed	Location	Institution	Recipient age/ gender	Immunotherapy	Graft survival	Patient survival	Acute rejection	Chronic rejection
Hand transplant									
Single hand transplant	February 1963	Guayaquil, Ecuador	(*)	28-year-old male	Cortisone/ 6-mercaptopurine/ azathioprine (AZA) and hydrocortisone	(–) 'Rejection and removal 3 weeks post-transplant; due to insufficient immunosuppression'	(+)	(+)	(–)
Single hand transplant	September 1998	Lyon, France	Hopital Edouard Herriot	48-year-old male	FK506/MMF/ prednisone	(–) 'Rejection and removal 2 years 4 months post-transplant; due to non-compliance'	(+)	(+)	(+)
Single hand transplant	January 1999	Louisville, USA	Jewish Hospital	37-year-old male	FK506/MMF/ prednisone	(+)	(+)	(+)	(–)
Single hand transplant	September 1999	Guangzhou, China	Nanfang Hospital	39-year-old male	FK506/MMF/ prednisone	(–) 'Rejection and removal 1 year 8 months post-transplant; unknown cause'	(+)	(+)	(–)
Single hand transplant	January 2000	Guangxi, China	First Affiliated Hospital of Guangxi University	27-year-old male	FK506/MMF/ prednisone	(+)	(+)	(*)	(–)
Double hand transplant	January 2000	Lyon, France	Hopital Edouard Herriot	33-year-old male	FK506/MMF/ prednisone	(+)	(+)	(+)	(–)
Digital transplant	January 2000	Yantai, China	Shandong Provincial Hospital	18-year-old male	(*)	(+)	(+)	(*)	(–)
Double hand transplant	March 2000	Innsbruch, Austria	Universitatsklinik fur Chirurgie	45-year-old male	(*)	(+)	(+)	(+)	(–)
Single hand transplant	May 2000	Kuala-Lumpur, Malaysia	Selayang Hospital	1-month-old female	None (Identical twin)	(+)	(+)	(–)	(–)
Double hand transplant	September 2000	Guangzhou, China	Nanfang Hospital		(*)	(+)	(+)	(*)	(–)
Single hand transplant	October 2000	Milano, Italy	Milano-Bicocca University	35-year-old male	(*)	(+)	(+)	(+)	(–)
Double hand transplant	January 2001	Harbin, China	First Affiliated Hospital of Harbin Medical University	(*)	(*)	(+)	(+)	(*)	(–)

Single hand transplant	February 2001	Louisville, KY, USA	Jewish Hospital	36-year-old male	(*)	(+)	(+)	(–)
Single hand transplant	October 2001	Milano, Italy	Milano-Bicocca University	(*)	FK506/MMF/ prednisone	(+)	(+)	(*)	(–)
Single hand transplant	June 2002	Brussels, Belgium	Erasme University Hospital	(*)	(*)	(+)	(+)	(*)	(–)
Single hand transplant	November 2002	Milan, Italy	Milano-Bicocca University	(*)	FK506/MMF/prednisone	(+)	(+)	(*)	(–)
Double hand transplant	February 2003	Innsbruch, Austria	Universitatsklinik fur Chirurgie	(*)	(*)	(+)	(+)	(*)	(–)
Double hand transplant	May 2003	Lyon, France	Hopital Edouard Herriot	(*)	FK506/MMF/prednisone	(+)	(+)	(*)	(–)
Face transplant									
Cephalocervical skin flap and two ears	September 2003	Nanjing, China	Jinling Hospital	72-year-old female	FK506/MMF/prednisone/ zenapax	(+)	(+)	(–)	(–)
Face transplant	November 2005	Aniens, France	Hopital Edouard Herriot	38-year-old female	FK506/MMF/prednisone	(+)	(+)	(+)	(–)
Face transplant	April 2006	Xi'an, China	Xijing Hospital	30-year-old male	FK506/MMF/prednisone	(+)	(+)	(*)	(–)

*Data unavailable.

skin graft from the same donor at a later date [10]. At the same time Medawar demonstrated that specific characteristics of the rejection process, such as latency, memory, and specificity of graft destruction, were the consequence of an active immune response mounted by the recipient [10]. These discoveries laid the groundwork for the development of the field of modern transplant immunology and earned Medawar the Nobel Prize in 1960. In the 1950s, Joseph Murray, a Plastic Surgeon, studied skin and kidney transplants in dogs and later went on to perform the first successful human kidney transplant between identical twins [12]. This landmark procedure sparked new interest in the field and led to many advances in solid organ transplantation. In 1990, Murray was awarded the Nobel Prize in Physiology/Medicine for his pioneering work in organ transplantation.

The late 1950s and early 1960s brought the discovery of several immunosuppressive agents such as azathioprine, 6-mercaptopurine and corticosteroids [13–16]. While in animal experiments these agents prolonged graft survival the dosages necessary to do so in CTA were toxic and often fatal. In 1963, a team of surgeons in Ecuador performed the first human hand transplant (Table 1). The immunosuppression used [azathioprine (AZA) and hydrocortisone] at the time was inadequate and the hand rejected within 3 weeks and was amputated [3,4].

In 1976, the introduction of cyclosporin A [17] ushered in a new era of transplantation. Animal studies followed by human studies using cyclosporin A in heart, kidney, pancreas and liver transplantation [18,19] demonstrated effective immunosuppression. These positive experiences in organ transplants led to several reports of small animal experiments in which CTAs in the form of hind limb and mandible bone transplants were performed and prolonged allograft survival was demonstrated [20–30]. In the late 1970s and early 1980s, three separate groups tested the efficacy of cyclosporin A in upper extremity transplants in primates [31–33]. Although rejection was suppressed for periods of up to 300 days, in these experiments the highly immunogenic skin portions of transplanted extremities were rejected within the first few months after transplantation. These discouraging results together with the failed human hand transplant in Ecuador caused reconstructive surgeons to abandon further attempts to transplant hands for another decade.

In the early 1990s, cyclosporin-AZA steroid-based regimens were used in a series of clinical CTAs to reconstruct nerves [34–37], tendons [38], muscle [39], bone and joint [40], and laryngeal defects [41]. In addition to the above listed procedures, more recently, additional CTAs have been reported in the clinical setting to reconstruct abdominal wall muscle [42], tongue [43,44; http://www.newscientist.com/article.ns?id=dn3964] and uterus

[45]. While the outcomes in these attempts have been reported to be generally positive, none of these CTAs contained skin and the associated appendages.

Human hand transplantation

In September of 1991, a conference on the clinical use of CTA was held in conjunction with the Rehabilitation Research and Development Service of the Department of the Veterans Affairs in Washington, DC. The purpose of the conference was to determine 'the clinical feasibility of transplanting limbs in patients with limb loss' and 'the direction in which clinically oriented limb transplantation research should head'. The conference participants concluded that CTA would be clinically possible in the near future and that 'historic' initial trials would occur over the next 2–5 years [46].

This prediction did not come to pass and 6 years later in November 1997 the 1st International Symposium on CTA was held in Louisville, Kentucky to discuss 'the barriers standing in the way of performing human hand transplants'. The meeting brought together leading experts in the fields of reconstructive surgery, transplant immunology, and medical ethics. The 2 days of discussions focused primarily on immunological and ethical barriers and while many opinions were aired, the overall consensus of those present at the meeting was that sufficient research had been done and the time had come to move hand transplantation research into the clinical arena. This was summed up in the closing remarks of the symposium's proceedings that concluded '…it is time to Just Do It' [47].

At the time of the 1997 CTA symposium in Louisville, the Plastic Surgery Research Laboratories at the University of Louisville hosting the meeting was actively engaged in animal research pursuing a variety of approaches focused on maximizing immunosuppression (because of the high immunogenicity of the skin) and minimizing their toxic side effects (because of the reluctance of hand surgeons to expose their amputee patients to the risks of immunosuppression). In keeping with these criteria several novel methods of local immunosuppressive drug delivery were explored. These included topical drug applications [48], direct drug delivery using implanted pumps [48–52] and magnetic drug targeting (attaching drugs to metal particles, infusing them systemically and then using a magnet placed over the transplanted allograft to localize the drug) [53,54]. Additional approaches that met the criteria of *maximal immunosuppression* with *minimal toxicity* were also studied; tolerance induction [55–58], low-dose immunosuppression [59] and lymph node removal [60,61].

In one of these experiments investigating local drug delivery using implanted pumps in a pig forelimb CTA model [62,63] the control group consisted of animals receiving a drug regimen, considered at the time, and still today, to be the gold standard in clinical kidney transplantation (tacrolimus/MMF/corticosteroid). Unexpectedly, the pumps (experimental group) malfunctioned, while the drug combination, (tacrolimus/MMF/corticosteroid), administered to the control animals effectively suppressed CTA 'skin' rejection for the duration of the experiment with relatively low toxicity. Based on these findings the University of Louisville team immediately applied to the hospitals' institutional review board for approval to perform 10 human hand transplants and at the same time presented their findings at an international hand surgery meeting in Vancouver [64]. These findings were subsequently published in a landmark paper [65].

Based on these findings, between 1998 and 1999, teams in Lyon (France) [66], Louisville (USA) [67] and Guangzhou (China) performed the first successful human hand transplants using tacrolimus/MMF/corticosteroid combination therapy [68]. At the time this manuscript was written, 24 hands (six double hand transplants and 12 single hand transplants) had been transplanted in 18 individuals world-wide. Seven of these are >7 years post transplant and only two graft failures have been reported, one due to noncompliance [69] and the other performed in China, because of unclear etiology [70].

Functional recovery

Overall the functional outcomes and patient satisfaction have been reported to be good [68,70] (Table 1). In all patients arterial blood supply and venous outflow have been reported to be satisfactory in the early post-transplant period and subsequently hands presented normal skin color and texture, and normal hair and nail growth.

Recovery of sensibility has been documented in all transplanted hands. The grade of sensory return paralleled results found in autologous replantation after trauma. In particular, protective sensation was achieved in all patients within 6–12 months and, as time progressed, 88% showed onset of more subtle discriminative sensation.

Recovery of motor function enabled the patients to perform most daily activities, including eating, driving, grasping objects, riding a bicycle or a motorbike, shaving, using the telephone, and writing. At 2 years all patients had returned to work, and improved manual skills allowed them not only to resume their previous jobs but also, in some cases, to find more suitable employment. This contributed to a reported improvement in quality of life in 83% of cases [68,70].

In spite of these promising early outcomes in this relatively small number of patients, debate continues over whether the risks associated with the immunosuppression drugs, required to prevent rejection are worth the benefits of hand transplantation. These risks are well known,

having been extensively studied in large populations of solid organ transplant recipients and more recently in the limited number of hand transplant recipients. Below we summarize the immunosuppression related risks reported in the hand transplant population.

Acute rejection

While it is not possible to predict long-term rejection in hand transplantation one can draw some conclusions from preliminary findings in the relatively small number of human hand transplants performed since 1998. At 1 year post-transplant, acute rejection rates have been reported to be 65% (excluding one transplant between identical twins), 11 of 17 allotransplants experienced a total of 26 rejection episodes) with tacrolimus/MMF/corticosteroid therapy [70]. In spite of this relatively high incidence of acute rejection all episodes were reported to have been successfully reversed and allograft and patient survival were 100% at 2 years post-transplantation. At a mean of 43 months, graft and patient survival were 89% and 100% respectively. As aforementioned, the two graft failures were reported to be due to noncompliance [69] with the reason for the other failure unclear [70].

These higher acute rejection rates in hand transplant recipients compared to kidney recipients receiving tacrolimus/MMF/corticosteroid therapy, are likely a result of the greater immunogenicity of the skin and its appendages [69,71–73] while the high allograft survival rates (despite relatively high acute rejection rates) may be due to increased diagnostic sensitivity and early recognition of (sub) acute rejection by visual skin inspection. The importance of early diagnosis of acute rejection has been demonstrated in clinical kidney transplantation. Current methods of monitoring acute rejection are relatively insensitive, resulting in delayed anti-rejection treatment and decreased long-term allograft survival. The significance of early diagnosis and treatment of acute rejection has been demonstrated in prospective studies of renal allograft biopsies [74] where unrecognized acute rejection was associated with an increased risk of chronic allograft nephropathy and late graft loss [75,76]. In contrast to solid organ transplants, acute rejection in hand transplants is manifested by early, visually apparent cutaneous changes that have a high correlation with histopathologic findings. Skin biopsies from co-transplanted 'distant sentinel skin flaps' can provide valuable adjunctive information regarding acute rejection with minimal patient morbidity [71,73].

Chronic rejection

While the exact mechanisms of chronic rejection have not been defined, both immunologic and non-immunologic factors have been implicated [55]. Experience from kidney transplantation has shown that (sub) acute rejection negatively affects renal allograft function [52,58,59] and survival [60,61]. However, in hand transplantation, this connection between subacute and chronic rejection has not yet been established.

In a single case clinical and histologic characterization of what was believed to be chronic (cutaneous) rejection was reported in the first human hand transplant recipient at the time his hand was surgically removed because of noncompliance. Examination of the rejected allograft demonstrated a histologic picture identical to chronic lichenoid GVHD [71,77].

In the other 16 hand transplant recipients chronic rejection has not been reported at a median follow-up of 43 months.

This low incidence of chronic rejection, even with concomitant high acute rejection rates [70] suggests that chronic rejection may not be as important a threat in hand as it is in renal transplantation [78,79]. Nevertheless, longer term follow-up and additional evaluations of chronic rejection in human hand and other CTAs are needed to better define its risk and influence on long term allograft function and survival.

Complications of immunosuppression

The primary complication associated with immunosuppressive therapy in the hand transplant population so far is infection. Complications such as malignancies, cardiovascular related disease, nephrotoxicity, gastrointestinal adverse effects and diabetes have not been reported [70]. Of the infections reported in hand transplant recipients, bacterial infection occurred at a rate of 12% (two infections: Clostridium difficile enteritis and Staphylococcus aureus osteitis), Fungal infections occurred in 28% (all cutaneous mycoses without invasive disease) and viral infection in 34% of cases. Only 6% of patients experienced cutaneous herpes simplex infections. None of these infections resulted in graft or patient loss [70]. Post-transplantation bone disease was reported in a single case of avascular necrosis of the hip. While post transplant diabetes mellitus has not been reported in hand transplant recipients, transient hyperglycemia occurred in 50% of the patients, primarily while receiving high corticosteroid doses early after transplantation [68,70]. Noncompliance was a problem in one of 18 patients and this could possibly have been avoided had a more careful pre-transplant psychosocial screening assessment been performed.

In conclusion, overall, with a post- transplant follow-up of 7 years in human hand transplantation the incidence of graft failure and complications has been low while functional and aesthetic recovery has been described as good.

Human face transplantation

To date, three cases of head and neck allotransplantation have been reported, two in China [80,81] and one in France [82,83] (Table 1). Facial transplantation has captured the interest and imagination of the media, scientists, and the lay public. Our face is much more than the anatomical location where our olfactory, auditory and visual organs are situated. We use facial expressions to communicate with the world around us and our face is the window through which others see and come to know us. It is this great importance we attach to our face that makes facial disfigurement such a devastating condition. Perception of the face dominates peoples' views of disfigured individuals and their facial appearance becomes their defining feature. Stevenage and McKay found in their research that job recruiters had a negative perception of facially disfigured applicants, which was associated with an adverse bias of work-related skills [84]. Facially disfigured individuals are frequently shut-ins, hiding from social relationships that others take for granted. They face a number of psychological and social problems, such as social anxiety, lowered self-confidence and self-esteem, negative self-image, depression, alcohol abuse, and marital problems [85–88]. Of all the physical handicaps, none is as socially devastating as facial disfigurement. In a large number of cases, facial disfigurement leads to depression, social isolation, and increased risk of suicide [85,89].

The positive early outcomes in human hand transplants encouraged and stimulated the team at the University of Louisville to apply their research and clinical experience to developing a program to perform human face transplants. The fact that the drug combination tacrolimus/MMF/corticosteroid effectively suppressed skin rejection both in their preclinical animal studies [64,65] and more importantly in their own [67] as well as other team's human hand transplants [68] meant that another major barrier to performing face transplants had been lowered.

The research team consulted with head and neck reconstructive surgeons, asking them what they felt was the greatest barrier standing in the way of performing facial transplantation; and they responded 'ethical and psychosocial issues' 'specifically those related to risk versus benefit'.

Based on this, the University of Louisville team shifted its research focus from investigating methods of suppressing CTA 'skin' rejection to defining the ethical parameters necessary to perform human face transplantation. To this end, they developed a strong multidisciplinary team including respected scientists and clinicians in the fields of psychology (body image), psychiatry, bioethics, sociology and plastic, head and neck, ophthalmologic and transplant surgery. Together they developed a set of *ethical guidelines* to guide their efforts and a research strategy to investigate *risk versus benefit issues in CTA*.

The first suggestion to the public that face transplantation was actually being considered as a clinical possibility stemmed from a presentation made by Mr Peter Butler, a consultant plastic surgeon at London's Royal Free Hospital in the UK, at the December 2002 meeting of the British Association of Plastic Surgeons [90]. He asserted that ten patients had approached him requesting facial transplants over the last year. Members of the media were in attendance, reporting on the event, and began to speculate that face transplant was indeed a clinical reality and this sparked media frenzy. This frenzy reached its height in Britain in December 2002 when the media singled out a young lady with facial disfigurement and reported that she had been selected by Mr Butler as the first face transplant recipient [91,92]. In response to this circus like atmosphere, James Partrige, the CEO of the well recognized support organization for facially disfigured 'Let's Face it', and a victim of facial disfigurement himself, called upon the Royal College of Surgeons (RCS) to 'create a moratorium on further media coverage of the issue' [44]. The RCS formed a 'Working Party on face transplantation' consisting of experts in the fields of Ethics, Reconstructive Surgery, Psychology and Transplantation to assess the current scientific merits of face transplantation.

On November 19th 2003, at the London Museum, at a much publicized 'Public Debate on the Feasibility of Face Transplantation' [93], Sir Peter Morris, the head of the RCS and chair of the Working Party recommended '…that until there is further research and the prospect of better control of complications it would be unwise to proceed with human facial transplantation'. The report ended welcoming comments in reponse to these findings [44].

In response to the RCS report, the University of Louisville team, who were also present and presented at the Public Debate at the London Museum, published their position [94]. Based on their own immunological and risk versus benefit research as well their experience in hand transplantation and the experience and research of others they concluded that the major technical, immunological and ethical barriers standing in the way of performing human facial transplantation had been overcome: and that 'in a select population of severely disfigured individuals facial transplantation, despite its recognized risks, could provide a better treatment option than current methods' and thus 'should move into its clinical research phase' [94]. Immediately following this, the same team in Louisville published their ethical guidelines for performing facial transplantation in the *American Journal of Bioethics* [94]. A key component of this set of ethical guidelines is 'Open Display and Public and Professional

Discussion and Evaluation'. To achieve this, the above cited publication invited experts from several related fields, including the surgical teams in the UK, France and at the Cleveland Clinic in the US to submit written commentaries critiquing these ethical guidelines. Fifteen commentaries [86,95–108] were published alongside the Louisville teams' ethical guidelines and their response to the commentaries [109]. Additional steps taken to promote 'Open Display and Public and Professional Discussion and Evaluation' included other scientific publications [47,110–112] and presentations to both scientific [102] and public audiences [93] as well as organizing forums for scientific discussion [113,114].

In keeping with their practice of 'Open Display and Public and Professional Discussion and Evaluation' in all of these forums, the University of Louisville team presented and discussed their position and more importantly listened to and learned from the positions of others. In this exercise of open discussion it became immediately apparent that the critics of face transplantation based their positions largely on theoretical discussions and their subjective opinions about the risk and benefits of this procedure. None of the vocal critics had actually referred to the direct life experiences of those confronting the risks of immunosuppression or had collected data from individuals who might benefit from different types of transplants. In contrast, the University of Louisville team expanded the risk versus benefit research they had begun with hand transplantation [115] to questions relevant to face transplantation. They developed and validated [116] a questionnaire-based instrument (Louisville Instrument for Transplantation; LIFT) to assess the amount of risk individuals would be willing to accept to receive different types of nonlife-saving transplant procedures (foot, single and double hand, larynx, hemi- and full face CTAs and kidney transplants). Using the LIFT, they questioned over 300 individuals with real life experiences in the risks of immunosuppression (kidney transplant recipients) [117] and individuals who could benefit from one of these procedures; limb amputees [118], laryngectomee patients [119] and individuals who had suffered facial disfigurement [120]. Of all those questioned in this series of studies, regardless of their individual life experience, all would risk the most to receive a face transplant. Of particular interest was the fact that they would risk even more to receive a face than a kidney transplant, which is considered standard care and for which there is no risk versus benefit debate. It was based on these findings that University of Louisville team took the position that the ethical barriers based on risk versus benefit had been lowered and the time had come to move facial transplantation research into the clinical arena [4,94].

In 2004, in preparation to perform clinical face transplants, a team in Paris France, led by Professor Laurent Lantieri submitted a proposal to the French government's advisory council on bioethics (Comit'e Consultatif National d'Ethique; CCNE). The council responded in a report entitled 'Composite tissue allotransplantation (CTA) of the face; full or partial facial transplant'. The report concluded that while it was not 'ethical' to perform a full face transplant at the time a partial face transplant (a triangle-shaped part of the face including the nose and mouth) could be performed [42].

Later, in October, 2005 an institutional review board at the Cleveland Clinic in Cleveland USA, approved a proposal submitted by a team at their hospital, led by Dr Maria Siemionow, to proceed with human face transplants [121] at which time the team began to screen potential patients. Also in 2005, in the US the American Society for Plastic Surgery (ASPS) and the American Society of Reconstructive Microsurgery (ASRM) issued their 'guiding principles' recommending 'that due to the unknown risks and benefits, those involved in this important work move forward in incremental steps' [122,123].

In September 2003 a team of surgeons at the Jinling Hospital in Nanjing, China transplanted a skin flap that included a large portion of posterior scalp and both ears from a donor onto a 72-year-old woman following the removal of a large cutaneous malignant melanoma (Table 1) [80]. While this transplant went relatively unnoticed by the scientific, medical and lay communities, many of the surgical, immunological and ethical issues and concerns of this procedure are present in facial transplantation and a great deal could be learned from following the outcomes in this patient. In November, 2005, in Amiens, France a surgical team led by Dr Bernard Devauchelle and Jean-Michel Dubernard announced that they had performed a partial face transplant on a 38-year-old female, whose face has been disfigured by a dog bite (Table 1). The surgery involved transplanting a triangular graft of tissue extending from the nose to the chin including the lips. 'Initial reports indicate that the recipient is doing well and both the medical community and the lay public have reacted favorably to the procedure' [82,83].

While it is too early to assess the functional outcome in this patient, early reports indicate that there is some return of movement and sensation. If this is true this mimics what has happened in the hand transplants where return of function was better than expected [68,70]. This effect is thought to be due to a collateral effect of accelerating nerve regeneration provided by the primary anti-rejection drug, tacrolimus, being used in these recipients [34]. While the anticipated functional recovery is not 100%, it is expected to be superior to that achieved with

conventional reconstructive methods (skin grafts, transplanted autologous tissues and facial prosthetics) in the population of patients being considered [109]. Immediately following this first clinical case, an ethics committees in the UK granted permission to Peter Butler at the Royal Free Hospital in London to perform facial transplants [121].

In April 2006 a team in Xi'an, capital of Shaanxi Province in northwest China, performed a face transplant on a 30-year-old male with facial disfigurement resulting from a bear bite. Initial reports indicate that the patient is doing well [124–126] (Table 1).

Hand and facial transplantation are now a clinical reality. As has been the case in so many advances in medicine, while these new treatments seem like an enormous lead forward, in reality the individual components necessary to accomplish these advancements have been around and routinely used in clinical practice for some time. The tissue transfer techniques used to transplant a hand or facial tissue, while complex, are used routinely to reattach amputated limbs and reconstruct complex facial defects. The immunosuppression medications used to prevent hand and facial tissue from rejecting have been used in thousands of organ transplant recipients. All of the logistics used to identify, select, harvest and transport the donor tissue has been developed and is used routinely in solid organ procurement. Then what is it that makes hand and face transplantation seem like such an enormous leap in medical advancement and what took the medical community so long to actually take this step? Perhaps, it is the fact that these treatments involve our hands and our face, parts of our anatomy that play such an important role in making us human.

The door has now been opened. As scientists and physicians it is now our duties to assure that hand and facial transplantation move into the clinical research phase in a thoughtful and well planned manner. To achieve this it is essential that teams proposing to perform these new procedures have the necessary technical and immunological expertise but more importantly that they develop and adhere to well-defined ethical guidelines. These guidelines should include open display and public and professional discussion and evaluation. By openly sharing and discussing our successes as well as our failures we will assure that this new and exciting medical frontier will reach mainstream medicine as quickly as possible and thus be made available to the many who suffer with these disfiguring deformities.

The role of clinical scientists is to gather as much knowledge as possible about new treatments from research, clinical experience, professional and public discussion and with this inform the patient and his/her family as best as is possible about the associated risks and benefits. Armed with this information it is ultimately the patient who must decide whether to be treated.

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