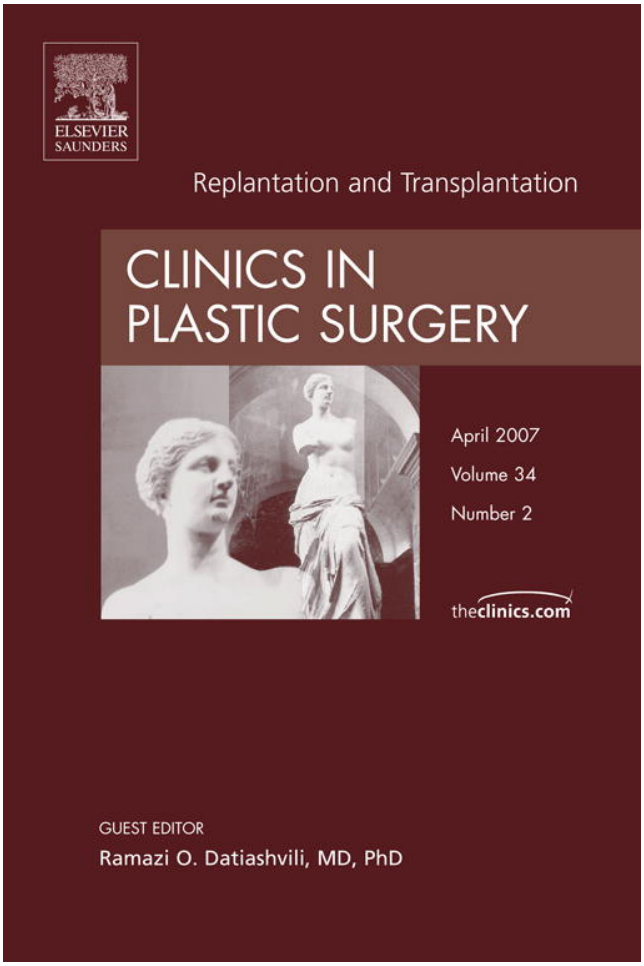

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Research and Events Leading to Facial Transplantation

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> Facial disfigurement from whatever cause is a challenge every day, as I soon discovered: being self-conscious in the extreme; a sense of 'standing out in the crowd;' of being stared at; asked curious questions; treated as odd and different; being name-called and avoided. Those affected can detect our disadvantage in small subtle (but not unseen) acts of eyes turning away or turning down.
>
> —James Partridge, a victim of facial disfigurement [1]

Facial transplantation has captured the interest and imagination of the media, scientists, physicians, and the lay public. Our face is much more than the anatomic 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 that we attach to our face that makes facial disfigurement such a devastating condition. Perception of the face dominates people's views of disfigured individuals, and their facial appearance becomes their defining feature. Stevenage and McKay [2] found that job recruiters had a negative perception of facially

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disfigured applicants, which was associated with a biased and adverse evaluation of work-related skills. Facially disfigured individuals are frequently shut-ins, hiding from social relationships that others take for granted. They suffer from a number of psychologic and social problems, such as social anxiety, lowered self-confidence and self-esteem, negative self-image, alcohol abuse, and marital problems [3–6]. Of all the physical handicaps, none seems as socially devastating as facial disfigurement. In a large number of cases, facial disfigurement leads not only to social isolation and unhappiness but clinical depression and increased risk of suicide [3,7].

Each year an estimated 7 million people in the United States need composite tissue reconstruction because of surgical excision of tumors, accidents, and congenital malformations [8]. This figure is more than double the number of solid organs needed for transplantation. Limb amputees comprise 1.2 million of these. According to government statistics, in the UK an estimated 390,000 people are disabled by disfigurement from trauma, mutilating surgery, skin disease, or birth defects; 250,000 of these suffer from facial disfigurement [9,10].

The fields of reconstructive and transplant surgery have enjoyed a close relationship throughout their development having worked closely together on some of the most important advances in their respective disciplines. One example is Joseph Murray [11], a plastic surgeon whose research in the 1950s on skin and kidney transplantation in dogs led him and his team to perform the first successful human kidney transplant between identical twins. This sparked new interest in the field, and in the half century that has passed since that landmark achievement, organ transplantation has become a standard treatment that has saved and improved the lives of over 400,000 people in the United States alone (United Network for Organ Sharing; http://www.unos.org). Today, Murray's pioneering work in transplantation is celebrated as one of the greatest advancements in modern medicine.

As the introduction of organ transplantation brought with it many challenges so has the introduction of composite tissue allotransplantation, particularly in the form of facial transplantation. This article discusses some of the major technical, immunologic, psychosocial, and ethical hurdles associated with facial transplantation. The authors provide an overview of the key research and events that have helped lower these hurdles and in doing so have ushered in a new era of reconstructive and transplant surgery.

In this article the authors: 1) discuss the limitations of conventional reconstructive methods for treating severe facial disfigurement, 2) review the history of composite tissue allotransplantation, 3) describe key research and events that led to human facial allotransplantation, and 4) reflect on critical issues that must be addressed to move facial transplantation toward becoming a treatment in mainstream medicine. A chronologic list of key research, events and, publications is provided in Table 1.

Limitations of conventional reconstructive surgery

In his 1979 editorial, "Logs vs. Harpsichords, Blobby Flaps vs. Finished Results," Frank McDowell challenged his colleague plastic surgeons to move their reconstruction skills to the next level: from covering tissue defects with "Blobby Flaps" to complete restoration of form and function or "finished results." In his words:

> What we need to see now are a few harpsichords, rather than so many logs—recognizable, new, artistic, and fully acceptable noses, cheeks, chins, necks, legs, and arms rather than indistinguishable globs and blobs of transported tissue in those areas. The manner in which we have proceeded was the only sensible way. One cannot sculpt a Venus de Milo, or any part of her, without moving a sufficient supply of satisfactory marble to the right location—and the ability to accomplish this had to come first. But there is a difference between being a hod carrier and a sculptor, and the time has come to produce more finished works of art—something that will not only function like a leg (or whatever) but also look like a leg (or whatever) [12].

Over the years advances in conventional reconstructive treatments have greatly improved the plastic surgeon's ability to cover large tissue defects and in many cases restore form and function. These reconstructive treatments consist of: 1) reattaching amputated body parts using microsurgical techniques, 2) transferring adjacent or distant autologous tissues to reconstruct tissue defects, and 3) using prosthetic materials to hide or disguise the tissue defect.

Replantation provides the best aesthetic and functional outcomes because the defect is reconstructed with the original tissues. However, this is often not possible because the tissue is destroyed beyond use (eg, burns, tumor extirpation) or because the tissue did not exist to begin with (eg, congenital anomalies). Although the latter two treatments (autologous tissues and prosthetics) do a good job of covering wounds, they are associated with several potential shortcomings, which include technical failure, infection, limited functional return, and poor cosmetic appearance. In addition, conventional reconstruction frequently requires staged surgeries and multiple revisions with resultant protracted rehabilitation. This slow process

Table 1: **Key events/publications leading to first human facial transplantations**

Date	Event	Location	Reference(s)
1963	First human hand transplantation followed by rejection and removal 3 weeks post transplant	Guayaquil, Ecuador	[27,151]
1986–92	Introduction of Cyclosporine A, brought new attempts to transplant hands in primate model. These attempts prolonged survival but failed due to high immunogenicity of skin.	Montreal, Canada Pittsburgh, PA Rotterdam, Netherlands	[38,39,152]
1994	Replantation of full facial tissues following degloving accident	Ludhiana, India	[153]
1995–97	Experiments in swine CTA, limb model demonstrate tacrolimus/mycophenolate mofetil Prednisone immunosuppression prevents "skin" rejection with relatively low toxicity.	Louisville, KY	[69,70]
1997	First International Symposium on Composite Tissue Allotransplantation	Louisville, KY	[52]
Sept-1998	Second human hand transplant—first to survive more than 2 years	Lyon, France	[71]
1999–2006	23 hands transplanted in 17 individuals	Worldwide	[75]
2000	Second International Symposium on Composite Tissue Allotransplantation	Louisville, KY	[128]
Jun 05	"Face Transplant" Documentry	—	[154]
Feb 2001	First hand transplant performed in Lyon, France Transplantation rejected and removed because of noncompliance	London, UK	[77]
1996–2000	Relevant publications before 2002 (6)	—	[70,72,73,100,153,155]
2002	Relevant ethics publications (2)	—	[156,157]
2002	Relevant immunology publications (1)	—	[129]
2002	Relevant surgical technique publications (1)	—	[158]
Dec 2002	Presentation by Mr. Peter Butler at British Association of Plastic Surgeons Meeting	London, UK	

(*continued on next page*)

Table 1: (*continued*)

Date	Event	Location	Reference(s)
Nov 2003	Public debate, "Feasibility of face transplant" at London Science Museum	London, UK	[93,159]
Nov 2003	Royal College of Surgeons Working Party report on facial transplantation released	London, UK	[94]
2003	Relevant ethics publications (3)	—	[160–162]
2003	Relevant immunology publications (2)	—	[74,163]
2003	Relevant surgical technique publications (3)	—	[147,164,165]
2004	Louisville team response to Royal College of Surgeons report	Louisville, KY	[13]
2004	Louisville team publishes Ethical Guidelines alongside invited commentaries and response	—	[4,101,109–121,127,166]
Jun 2005	French Ethics Committee, releases position paper on facial transplantation	Paris, France	[142]
2004	Relevant ethics publications (39)	—	[4,13,101,104–107, 109–127,166–178]
2004	Relevant immunology publications (3)	—	[179–181]
2004	Relevant surgical technique publications (2)	—	[182,183]
Sep-2004	Human cephalocervical skin flap and two ears allotransplant performed	Nanjing, China	[95]
Oct 2004	Cleveland Clinic team in the United States receives Institutional Review Board approval to perform human facial transplantation	Cleveland, OH	[143]
2005	Ethics publications (11)	—	[184–194]
2005	Relevant immunology publications (2)	—	[195,196]
2005	Relevant surgical technique publications (5)	—	[75,98,197–199]
Nov 2005	First human facial transplantation performed	Amiens, France	[98]
Dec 2005	Mr. Peter Butler receives approval to perform human facial transplantations in the UK	London, UK	[143,200]

(*continued on next page*)

Table 1: (*continued*)

Date	Event	Location	Reference(s)
Jan 2006	American Society of Reconstructive Microsurgery and American Society for Plastic Surgery release facial transplantation "Guiding Principles"	—	[144,145]
Apr 2006	Second human facial transplantation performed	Xi'an, China	[96]
Jan–June 2006	Relevant ethics publications (23)	—	[138,139,141, 143–146,201–216]
Jan–June 2006	Relevant immunology publications (2)	—	[217,218]
Jan–June 2006	Relevant surgical technique publications (8)	—	[99,139,202,219–222]

Data from Gander B, Brown CS, Vasilic D, et al. Composite tissue allotransplantation of the hand and face: a new frontier in transplant and reconstructive surgery. Transpl Int 2006;19:868–880.

often impedes returning to work and normal life. All of these factors place a tremendous burden on patients, their families, the health care system, and ultimately society, which must absorb the financial cost of multiple procedures, prolonged rehabilitation, and loss of work productivity.

Composite tissue allotransplantation (CTA), and in particular facial transplantation, could provide superior functional and aesthetic results and thus eliminate the drawbacks of traditional reconstructive methods. Rather than multiple surgeries over many years, facial transplantation could make it possible to perform one major surgery followed by a few smaller revisions as necessary achieving superior aesthetic and functional outcomes [13].

The history of composite tissue allotransplantation

Long before solid organ transplantation was considered, CTA was making history. In 348 AD "The legend of the black leg" 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 [14]. Upon awakening, the man discovered that his disease-ridden leg had been replaced by a healthy "black" leg [15]. This legend has been immortalized in several paintings by a number of fifteenth-century artists [16].

In the sixteenth century, in Bologna Italy, Gaspare Tagliacozzi, (1547–1599), considered by many to be the father of modern plastic surgery, described transplanting the nose from a slave to his master. The story goes that the slave donated his nose in exchange for his freedom. The interesting but apocryphal outcome was that the death of the slave 3 years later coincided with the rejection of the transplanted nose [17]. Subsequently several reports of tissue transplantations appeared periodically in the literature. The first substantiated successful allotransplantation was that of sheepskin reported by Bunger [18] in 1804. This work contributed to the concept of transplanting "skin grafts."

In the early 1900s, Alexis Carrel [19] described successful orthotopic hind limb and kidney transplantations in dogs. This was the era of Henry Ford, Thomas Edison, and the Wright Brothers, and the public was easily able to imagine how scientific advancements could lead to major changes in daily life. At the time human organ transplantation and other revolutions in surgery did not seem far off. For his pioneering work, Carrel was awarded the Nobel Prize in 1912 [20]. 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 [21]. Although Carrel's and Guthrie's work laid the foundation for the development of the surgical techniques (nerve and vessel anastomisis) necessary to transplant tissues and organs, the immunologic barriers were yet to be addressed.

The tragedies of war provided the impetus for the first studies of the immunologic barriers associated with tissue allotransplantation. Large numbers of severely burned fighter pilots in the Battle of Britain in World War II was the catalyst for the formation of

a burn unit at the Glasgow Royal Infirmary. A young plastic surgeon, Thomas Gibson, was hired by the British Medical Research Council to care for these pilots. Gibson [22] noted accelerated rejection of skin grafts from the same donor that were transplanted on a second attempt at a later date. He worked with Peter Medawar, a Zoologist and researcher [22] who, in animal experiments, demonstrated that specific characteristics of the rejection process (ie, latency, memory, and specificity of graft destruction) were the consequence of an active immune response mounted by the recipient. These discoveries laid the groundwork for the development of the field of modern transplant immunology and the subsequent development of immunotherapy used today to prevent rejection of allotransplant tissues. Medawar received the Nobel Prize in 1960 for his research.

In the 1950's, plastic surgeon, Joseph Murray conducted research into the surgical and immunologic aspects of skin and kidney transplantation using a dog model. On December 23rd, 1954, Murray [11] led a team doctors who applied this research in performing the first successful human kidney transplant between identical twins. 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 [23–26]. Although these agents prolonged graft survival in animal experiments, 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 agents used at the time, azathioprine and hydrocortisone, were inadequate and the hand rejected within 3 weeks and was amputated [27].

In 1976 the introduction of cyclosporine A [28] ushered in a new era of transplantation. Animal studies followed by human studies using cyclosporine A in heart, kidney, pancreas, and liver transplantation [29,30] demonstrated effective immunosuppression. Cyclosporine-based immunosuppression caused acute rejection rates to fall from above 70% to less than 50% [31]. These positive experiences in organ transplantations 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 [32–37].

In the late 1970s and early 1980s, three groups tested the efficacy of cyclosporine A in upper extremity transplants in primates [38–40]. 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 and had to be removed. 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, cyclosporine-azathioprine steroid-based regimens were used in a series of clinical CTAs to reconstruct nerves [41–43], tendons [44], muscle [45], bone and joint [46], and laryngeal defects [47]. More recently, additional CTAs have been reported in the clinical setting to reconstruct abdominal wall muscle [48], tongue [49], and uterus [50]. Although the outcomes in these attempts have been generally positive, none of these CTAs contained skin and its associated appendages.

Research and events leading to human facial transplantation

Perhaps the single most important development that allowed facial transplantation to be considered as clinically feasible was the early success of human hand transplantation. Many of the same technical, immunologic, psychosocial and ethical barriers that were overcome to perform human hand transplants served to pave the way for performing human facial transplantation. Accordingly, the remainder of this article discusses key research and events that led to human hand, and then facial, transplantation.

In September 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 to 5 years [51]. This prediction did not come to pass. Six years later, in November 1997, the First 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-day event focused primarily on immunologic and ethical barriers. Although many opinions were aired, the overall consensus at the meeting was that sufficient animal 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.'" [52]

At the time of the 1997 CTA symposium in Louisville, the Plastic Surgery Research Laboratories at the University of Louisville, who hosted the symposium, were 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 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 [53], direct drug delivery using implanted perfusion pumps [53–57], and magnetic drug targeting (ie, attaching drugs to metal particles, infusing them systemically, and then using magnets placed over the transplanted allograft to localize the drug) [58,59]. Additional approaches that met the criteria of maximal immunosuppression with minimal toxicity were also studied: tolerance induction [60–63], low dose immunosuppression [64], and lymph node removal [65,66]. One of these experiments compared local drug delivery using implanted pumps in a pig forelimb CTA model [67,68] in which the control group consisted of animals receiving a 3-drug regimen (tacrolimus/mycophenolate mofetil/corticosteroid) considered to be the gold standard in clinical kidney transplantation. The experimental group's pumps malfunctioned, but the drug combination administered to the control animals was unexpectedly effective in suppressing CTA "skin" rejection with relatively low toxicity for the duration of the experiment. Based on these findings, the University of Louisville team immediately applied to the hospital's institutional review board for approval to perform human hand transplantation and presented their findings at an international hand surgery meeting in Vancouver [69]. These findings were subsequently published in a landmark paper [70].

Using this drug combination (tacrolimus/mycophenolate mofetil/corticosteroids) in 1998 and 1999 teams in Lyon, France [71], Louisville, Kentucky [72], and Guangzhou, China performed the first successful human hand transplants [73]. At the time the present manuscript was written, 23 hands (6 double hand transplants and 11 single hand transplants) had been transplanted in 17 individuals worldwide. Several of these are more than 7 years posttransplantation, and only 2 graft failures have been reported: one in France due to patient noncompliance [74,76] and the other in China due to unclear etiology [75].

Functional recovery

Overall, functional outcomes and patient satisfaction in hand transplantation have been good [73,75]. In all patients in the early posttransplantation period, arterial blood supply and venous outflow have been satisfactory, with 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 to 12 months, and, as time progressed, 88% showed the 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. Overall, these outcomes contributed to a reported improvement in quality of life in 83% of cases [73,75].

Acute rejection

Although it is not possible to predict long-term rejection in hand transplantation, one can draw conclusions from preliminary findings in the small number of human hand transplants (n = 24 on 18 patients) performed since 1998. At 1-year posttransplantation, acute rejection rates have been 65% (excluding one transplantation between identical twins); 11 out of 17 hand transplant recipients experienced a total of 26 rejection episodes with tacrolimus/mycophenolate mofetil/corticosteroid therapy [75]. In spite of this high incidence of acute rejection, all episodes were successfully reversed, and allograft and patient survival were 100% at 2 years posttransplantation. At a mean of 43 months posttransplantation, graft and patient survival were 89% and 100%, respectively, with 2 of 18 graft failures. The higher acute rejection rates in hand transplant recipients compared with kidney recipients receiving tacrolimus/mycophenolate mofetil/corticosteroid therapy are likely a result of the greater immunogenicity of the skin and its appendages [74,77–79]. By contrast, 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 in internal organs are relatively insensitive, resulting in delayed antirejection

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 [80] whereby unrecognized acute rejection was associated with an increased risk of chronic allograft nephropathy and late graft loss [81,82]. In contrast to solid organ transplantations, acute rejection in transplanted hands is manifested by early, visually apparent cutaneous changes that have a high correlation with histopathologic findings [77,79].

Chronic rejection

Although the exact mechanisms of chronic rejection have not been defined, both immunologic and nonimmunologic factors have been implicated [83]. Experience from kidney transplantation has showed that (sub)acute rejection negatively affects renal allograft function and survival [84,85]. However in hand transplantation, this connection between (sub)acute 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 recipient of the hand transplant performed in 1998 in Lyon France after he stopped taking his immunosuppression medications and his was surgically removed. Examination of the rejected allograft demonstrated a histologic picture identical to chronic lichenoid graft versus host disease [77,86]. In the remaining 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 [75], suggests that chronic rejection may not be as important a threat in hand as it is in renal transplantation [87,88]. 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 [89].

Complications of immunosuppression

The primary complication associated with immunosuppressive therapy in the hand transplant population, so far, has been infection. Complications such as malignancies, cardiovascular related disease, nephrotoxicity, gastrointestinal adverse effects, and diabetes have not been reported [75]. 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 [75]. Posttransplantation bone disease was reported in a single case of avascular necrosis of the hip. Although posttransplantation 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 [73,75]. Noncompliance was a problem in 1 of 18 patients and this could possibly have been avoided had a more careful pretransplantation psychosocial screening assessment been performed. Overall, with a posttransplantation follow-up of 7 years in human hand transplantation, the incidence of graft failure and complications has been low whereas functional and aesthetic recovery has been described as good.

Human facial transplantation

The first suggestion to the public that facial transplantation was a clinical possibility stemmed from a presentation made by 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 10 patients had approached him requesting facial transplantations over the last year. The news media, which were present at the event, reported that facial transplantation was indeed a clinical reality and speculated that Butler's team in the United Kingdom was racing a team in the United States to become the first to perform the procedure. This sparked a media frenzy that reached its height in Britain when the media singled out a young lady who had facial disfigurement and reported that Peter Butler had selected her 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 called "Changing Faces," and a victim of facial disfigurement himself, called upon the Royal College of Surgeons to create a moratorium on further media coverage of the issue. The Royal College of Surgeons formed a "working party on facial transplantation" consisting of experts in the fields of ethics, reconstructive surgery, psychology and transplantation to assess the current scientific merits of facial transplantation. On November 19, 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 Royal College of Surgeons 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 on these findings [94].

In response to the Royal College of Surgeons' report, the University of Louisville team, who were also present at the Public Debate at the London Museum, presented and subsequently published [13] their position: "the major technical, immunologic 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."

To date, three cases of head and neck allotransplantation have been reported: two in China [95,96] and one in France [97–99] (**Table 1**). The positive early outcomes in human hand transplantation encouraged and stimulated the team at the University of Louisville to apply their research and clinical experience to developing a program to perform human facial transplantations. The fact that the drug combination tacrolimus/mycophenolate mofetil/Prednisone effectively suppressed skin rejection in their preclinical animal studies [69,70] and in their own [72], as well as in other team's hand transplants [73], meant that another major barrier to performing human facial transplantations had been lowered.

The research team consulted with head and neck reconstructive surgeons, asking them what they felt was the greatest barrier to performing facial transplantation, and they responded "ethical and psychosocial issues…specifically those related to risk versus benefit." Thus, 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 facial transplants. 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 direct their efforts and a research strategy to investigate risk versus benefit issues in CTA.

Ethical guidelines

Ethical guidelines for performing facial transplantation were developed by expanding a set of guidelines they created in 1997 while preparing to perform human hand transplants [100]. These ethical guidelines stipulate that eight criteria should be met before moving forward with facial transplantation [101]. Francis Moore [102,103] proposed four of these criteria in the late 1980s for introducing innovative surgical procedures:

1. *Scientific background in the innovation:* The preparatory scientific groundwork should have been laid through laboratory and clinical research on the pertinent medications, technology, procedures, and ethical issues.
2. *Skill and experience of the team:* The surgeons and clinicians involved in the research must possess the knowledge, experience, skills, and technical abilities needed to perform the procedure safely.
3. *Open display, and public and professional discussion and evaluation:* Before performing the procedure, a team's plans should be openly publicized and discussed with professional and lay communities, thereby allowing their input. Moreover, the research team must seriously consider this input so that when appropriate it may influence the revision of the research proposal (see later discussion).
4. *Ethical climate of the institution:* The innovation is not being performed for purposes of institutional prestige or professional recognition. Instead, it should be the criteria enumerated here that drives the innovation.

An additional four ethical criteria which are commonly applied to health care research were added [101].

5. *Sufficient animal research performed:* Sufficient preclinical research must have been done to justify moving the research into humans. This is a specific elaboration of item 1.
6. *Informed and willing subjects:* There should exist informed subjects who, deeming the procedure beneficial, want to undergo it and who will lose the benefits if it is postponed to wait for further developments.
7. *An important existing need for the treatment:* There exist many other potential subjects who could, in the future, benefit from this procedure if it proves to be successful.
8. *Regulatory approval:* The procedure has been subjected to the established regulatory scrutiny and reviews, including approval by the relevant Institutional Review Board for the Protection of Human Subjects.

These ethical guidelines were developed to channel the Louisville team's research efforts and were proposed as a framework for other teams preparing to perform facial transplantation. If these eight criteria are satisfied, the Louisville team submits that it is justified to perform this experimental procedure on qualified, voluntary, and informed human subjects.

Open display and public and professional discussion and evaluation are key components of these

ethical guidelines (item 4). To achieve this, on two separate occasions, the Louisville team published their views on facial transplantation in the International Journal of Surgery [13] and The American Journal of Bioethics [101]. In both cases, the journals solicited written critiques by experts in related fields, which were published along with the Louisville team's "target" article [4,104–121] and that group's response to the critiques [122–127]. In these publications, written critiques were solicited from the surgical teams in the United Kingdom, France, and at the Cleveland Clinic in Cleveland, Ohio, who themselves were preparing to perform the procedure. Additional steps were taken to promote open display and public and professional discussion and evaluation, which included other scientific publications [52,128–132] and presentations to both scientific [133,134] and public audiences [93], web-based public discussions (http://www.danacentre.org.uk/events/2003/11) as well as organizing forums for scientific discussion [135,136]. 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 listened to and learned from the positions of others.

Through this exercise it became immediately apparent that the critics of facial transplantation based their positions largely on theoretic conjectures and their subjective opinions about the risk and benefits of the procedure. None of the vocal critics 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. Accordingly, the University of Louisville team developed and validated a questionnaire-based instrument (Louisville Instrument for Transplantation) [137] to assess the amount of risk that individuals would be willing to accept to receive different types of non–life-saving transplant procedures (foot, single and double hand, larynx, hemi- and full-facial CTA's and kidney transplantations). Using the Louisville Instrument for Transplantation, they surveyed over 300 individuals with real-life experiences in the risks of immunosuppression (kidney transplant recipients) [138] and individuals who could benefit from one of these procedures: limb amputees [139], laryngectomee patients [140], and individuals who had suffered facial disfigurement [141]. They also questioned plastic and transplant surgeons with extensive experience treating facially disfigured and organ transplant recipients respectively. All of the populations questioned in this series of studies, regardless of their individual life experience, indicated that they would risk the most to receive a facial transplant. They would risk even more to receive a facial than a kidney transplant which is considered standard care and for which there is no risk versus benefit debate. Thus, the University of Louisville team took the position that the ethical barriers based on risk versus benefit had been carefully considered, and the time had come to move facial transplantation research into the clinical arena [13,101].

In 2004, in preparation to perform clinical facial transplants, a team in Paris, France, led by Laurent Lantieri submitted a proposal to the French government's advisory council on bioethics (Comit'e Consultatif National d'Ethique). The council responded in a report entitled "Composite tissue allotransplantation of the face; full or partial facial transplant." The report concluded that although it was not "ethical" to perform a full-facial transplant, a partial facial transplant (including a triangle shaped part of the face that includes the nose and mouth) could be performed [142]. Later, in October 2005, an institutional review board at the Cleveland Clinic in Cleveland, Ohio approved a proposal submitted by a team at their hospital, to proceed with human facial transplantation [143], at which time the team began to screen potential patients. Also in 2005, the American Society for Plastic Surgery and the American Society of Reconstructive Microsurgery issued their "guiding principles" recommending "that due to the unknown risks and benefits, those involved in this important work move forward in incremental steps" [144–146].

In September 2004, a team of surgeons in Nanjing, China performed an allotransplant of a large cephalocervical skin flap that included both ears in a 72-year-old woman. The surgery was to reconstruct a large defect created by the removal of a melanoma [147]. Although this surgery did not receive much attention from the scientific or lay communities, there existed a great deal of technical, immunologic and ethical overlap with facial transplantation, and much could be learned by following the outcomes closely (**Table 1**). A year later in November 2005, in Amiens, France a surgical team led by Bernard Devauchelle and Jean-Michel Dubernard announced that they had performed a partial facial transplant on a 38-year-old female, whose face had 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" [97–99]. Although it is too early to assess the functional outcome, early reports indicate that there is return of movement and sensation. If these results hold, they mimic what happened in the hand transplantation experience whereby

return of function was better than expected [73,75]. This may be due to a collateral effect of accelerating nerve regeneration provided by the primary antirejection drug, tacrolimus, being used in these recipients [42]. Although the anticipated functional recovery in facial transplantation 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 [127].

Immediately following reports of the facial transplant in France, a hospital ethics committee in the United Kingdom granted permission to Peter Butler's team at the Royal Free Hospital in London to perform facial transplantation [143].

In April 2006, a team in Xi'an, capital of Shaanxi Province in northwest China, performed a facial transplant on a 30-year-old male who had facial disfigurement resulting from a bear bite. Initial reports indicate that the patient is doing well (**Table 1**) [148–222].

Moving this new frontier into mainstream medicine

Facial transplantation is now a clinical reality. Although this new treatment seems like an enormous leap forward, in reality many of the individual components necessary to accomplish this advancement have been available and routinely used in clinical practice for some time. The tissue transfer techniques used to transplant facial tissue, while complex, are used routinely to 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 donor tissues have been developed and are used routinely in solid organ procurement. That being the case, what is it that makes facial 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 because this procedure involves the face, a part of our anatomy that is so central to identity and plays such an important role in making us human. The misconception that transplanting another individual's face onto one's own would in fact change the identity of the recipient is frightening to many. But in fact, most patients who have severe facial disfigurement lost their former identity with their injury. The identity they live with today is the "starting point" and is what they seek improvement over.

The door has now been opened. As scientists and physicians, it is now our duties to assure that facial transplantation moves into the clinical research phase in a thoughtful and well-planned manner. To achieve this, it is essential that teams proposing to perform this new procedure have the necessary technical and immunologic 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 both our successes and 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 so many who suffer with these disfiguring deformities.

As plastic surgeons we have learned how to "move a sufficient supply of satisfactory marble to the right location." Now, more than 25 years after Dr. McDowell's challenge, perhaps, working together with transplant surgeons, plastic surgeons will use facial transplantation to become "sculptors" and "produce more finished works of art" by creating "a few harpsichords, rather than so many logs…" [12].

References

[1] Partridge J. Discovering resilience: supporting children and families with facial differences. Presented at the Face of the Child: Surgeon General's Conference on Children and Oral Health. Washington, DC, June 12–13, 2000. Available at: http://www.google.com/search?hl=en&lr=&q=Discovering+Resilience%3A+Supporting+Children+and+Families+with+Facial+differences+James+Partridge&btnG=Search. Accessed August 29, 2006.

[2] Stevenage S, McKay Y. Model applicants: the effect of facial appearance on recruitment decisions. Br J Psychol 1999;90:221–34.

[3] Robinson E, Rumsey N, Partridge J. An evaluation of the impact of social interaction skills training for facially disfigured people. Br J Plast Surg 1996;49:281–9.

[4] Rumsey N. Psychological aspects of face transplantation: read the small print carefully. Am J Bioeth 2004;4:22–5 [discussion: W23–31].

[5] Levine E, Degutis L, Pruzinsky T, et al. Quality of life and facial trauma: psychological and body image effects. Ann Plast Surg 2005;54:502–10.

[6] Pruzinsky T, Levine E, Persing J, et al. Facial trauma and facial cancer. Philadelphia: Lippincott Williams and Wilkins; 2006.

[7] Ye EM. Psychological morbidity in patients with facial and neck burns. Burns 1998;24:646–8.

[8] Langer R, Vacanti JP. Tissue engineering. Science 1993;260:920–6.

[9] Martin J, Meltzer H, Elliot D, (1988). OPCS surveys of disability in Great Britain, report 1: the prevalence of disability among adults. London: HMSO.

[10] Newell R, Marks I. Phobic nature of social difficulty in facially disfigured people. Br J Psychiatry 2000;176:177–81.
[11] Murray JE. Surgery of the soul: reflections on a curious career. Chapter 9. Canton (MA): Watson Publishing International. 2001. p. 73–87.
[12] McDowell F. Logs vs. harpsichords, blobby flaps vs. finished results. Plast Reconstr Surg 1979;64: 249.
[13] Barker J, Vossen M, Banis J. The technical, immunological and ethical feasibility of face transplantation. International Journal of Surgery 2004;2:8–12.
[14] Zimmermann KW. One Leg in the grave: the miracle of the transplantation of the black leg by the Saints Cosmas and Damian. Maarssen, Holland: Elsevier/Bunge, Maarssen, 1998.
[15] Kann BR, Furnas DW, Hewitt CW. Past, present, and future research in the field of composite tissue allotransplantation. Microsurgery 2000;20: 393–9.
[16] Zimmermann KW. One leg in the grave: the miracle of the transplantation of the black leg by the saints Cosmas and Damian. Maarssen (the Netherlands): Elsevier/Bunge; 1998.
[17] Gnudi MT, Webster JP. The life and times of Gespare Tagliacozzi, surgeon of Balogna. New York: Herbert Reichner; 1950:282.
[18] Bunger C. Gelungener versuch einer nasenbildung aus einem vollig getrennten hautstuck aus dem beine. [Original article in German. Transplanted: Successful nose construction using a free skin flap from the leg.] J Chir Augenheilk 1823;4:569.
[19] Carrel A. Landmark article, Nov 14, 1908: results of the transplantation of blood vessels, organs and limbs. By Alexis Carrel. JAMA 1983; 250:944–53.
[20] Toledo-Pereyra LH. Classics of modern surgery: the unknown man of Alexis Carrel—father of transplantation. J Invest Surg 2003;16:243–6.
[21] Guthrie C. Applications of blood vessels surgery. In: Blood vessel surgery of blood vessels surgery. London: Edward Arnold; 1912. p. 222–93.
[22] Gibson T, Medawar PB. The fate of skin homografts in man. J Anat 1943;77:299–310.
[23] Goldwyn RM, Beach PM, Feldman D, et al. Canine limb homotransplantation. Plast Reconstr Surg 1966;37:184–95.
[24] Lance EM, Inglis AE, Figarola F, et al. Transplantation of the canine hind limb. Surgical technique and methods of immunosuppression for allotransplantation. A preliminary report. J Bone Joint Surg Am 1971;53:1137–49.
[25] Goldberg VM, Porter BB, Lance EM. Transplantation of the canine knee joint on a vascular pedicle. A preliminary study. J Bone Joint Surg Am 1980;62:414–24.
[26] Doi K. Homotransplantation of limbs in rats. A preliminary report on an experimental study with nonspecific immunosuppressive drugs. Plast Reconstr Surg 1979;64:613–21.
[27] Gilbert R. Transplant is successful with a cadaver forearm. Med Trib Med News 1964;5:20.
[28] Borel JF, Feurer C, Gubler HU, et al. Biological effects of cyclosporin A: a new antilymphocytic agent. Agents Actions 1994;43:179–86.
[29] Morris PJ. Cyclosporin A. Transplantation 1981; 32:349–54.
[30] Calne RY, Rolles K, White DJ, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979;2:1033–6.
[31] [No authors listed]. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. N Engl J Med 1983;309:809–15.
[32] Press B, Sibley R, Shons A. Limb allotransplantation in the rat: extended survival and return of nerve function with continuous cyclosporine/prednisone immunosuppression. Ann Plast Surg 1986;16:313–21.
[33] Hewitt CW, Black KS, Fraser LA, et al. Composite tissue (limb) allografts in rats. I. Dose-dependent increase in survival with cyclosporine. Transplantation 1985;39:360–4.
[34] Siliski JM, Simpkin S, Green CJ. Vascularized whole knee joint allografts in rabbits immunosuppressed with cyclosporin A. Arch Orthop Trauma Surg 1984;103:26–35.
[35] Fritz WD, Swartz WM, Rose S, et al. Limb allografts in rats immunosuppressed with cyclosporin A. Ann Surg 1984;199:211–5.
[36] Kniha H, Randzio J, Gold ME, et al. Growth of forelimb allografts in young rabbits immunosuppressed with cyclosporine. Ann Plast Surg 1989;22:135–41.
[37] Randzio J, Kniha H, Gold ME, et al. Growth of vascularized composite mandibular allografts in young rabbits. Ann Plast Surg 1991;26: 140–8.
[38] Daniel RK, Egerszegi EP, Samulack DD, et al. Tissue transplants in primates for upper extremity reconstruction: a preliminary report. J Hand Surg [Am] 1986;11:1–8.
[39] Stark GB, Swartz WM, Narayanan K, et al. Hand transplantation in baboons. Transplant Proc 1987;19:3968–71.
[40] Hovius SE, Stevens HP, van Nierop PW, et al. Allogeneic transplantation of the radial side of the hand in the rhesus monkey: I. Technical aspects. Plast Reconstr Surg 1992; 89:700–9.
[41] Bain JR. Peripheral nerve and neuromuscular allotransplantation: current status. Microsurgery 2000;20:384–8.
[42] Mackinnon SE, Doolabh VB, Novak CB, et al. Clinical outcome following nerve allograft transplantation. Plast Reconstr Surg 2001;107: 1419–29.
[43] Mackinnon SE. Nerve allotransplantation following severe tibial nerve injury. Case report. J Neurosurg 1996;84:671–6.
[44] Guimberteau JC, Baudet J, Panconi B, et al. Human allotransplant of a digital flexion system

vascularized on the ulnar pedicle: a preliminary report and 1-year follow-up of two cases. Plast Reconstr Surg 1992;89:1135–47.
[45] Jones TR, Humphrey PA, Brennan DC. Transplantation of vascularized allogeneic skeletal muscle for scalp reconstruction in renal transplant patient. Transplant Proc 1998;30:2746–53.
[46] Hofmann GO, Kirschner MH. Clinical experience in allogeneic vascularized bone and joint allografting. Microsurgery 2000;20:375–83.
[47] Strome M, Stein J, Esclamado R, et al. Laryngeal transplantation and 40-month follow-up. N Engl J Med 2001;344:1676–9.
[48] Levi DM, Tzakis AG, Kato T, et al. Transplantation of the abdominal wall. Lancet 2003;361: 2173–6.
[49] Bhattacharya S. First human tongue transplant successful. 2003 Available at: http://www.newscientist.com/article.ns?id=dn3964. Accessed April 29, 2006.
[50] Fageeh W, Raffa H, Jabbad H, et al. Transplantation of the human uterus. Int J Gynaecol Obstet 2002;76:245–51.
[51] Black K, Hewitt C. Composite tissue transplantation workshop. Washington, DC: Department of Veterans Affairs, Rehabilitation Research and Development Service; 1991.
[52] Barker J, Jones J, Breidenbach W. Composite tissue transplantaton: a clinical reality? Transplant Proc [Invited Editor] 1998;30:2686–787.
[53] Shirbacheh MV, Jones JW, Breidenbach WC, et al. The case for local immunosuppression in composite tissue allotransplantation. Transplant Proc 1998;30:2739–42.
[54] Shirbacheh MV, Ren X, Jones JW, et al. Pharmacokinetic advantage of intra-arterial cyclosporin A delivery to vascularly isolated rabbit forelimb. I. Model development. J Pharmacol Exp Ther 1999;289:1185–90.
[55] Shirbacheh MV, Jones JW, Harralson TA, et al. Pharmacokinetics of intra-arterial delivery of tacrolimus to vascularly isolated rabbit forelimb. J Pharmacol Exp Ther 1999;289:1196–201.
[56] Shirbacheh MV, Harralson TA, Jones JW, et al. Pharmacokinetic advantage of intra-arterial cyclosporin A delivery to vascularly isolated rabbit forelimb. II. Dose dependence. J Pharmacol Exp Ther 1999;289:1191–5.
[57] Gruber SA, Shirbacheh MV, Jones JW, et al. Local drug delivery to composite tissue allografts. Microsurgery 2000;20:407–11.
[58] Lubbe AS, Bergemann C, Riess H, et al. Clinical experiences with magnetic drug targeting: a phase I study with 4′-epidoxorubicin in 14 patients with advanced solid tumors. Cancer Res 1996;56:4686–93.
[59] Lubbe AS, Bergemann C, Huhnt W, et al. Preclinical experiences with magnetic drug targeting: tolerance and efficacy. Cancer Res 1996; 56:4694–701.
[60] Prabhune KA, Gorantla VS, Maldonado C, et al. Mixed allogeneic chimerism and tolerance to composite tissue allografts. Microsurgery 2000; 20:441–7.
[61] Gorantla V, Perez-Abadia G, Prabhune K, et al. Composite tissue allograft (CTA): tolerance induction without graft vs host disease. Surg Forum 2000;51:578–9.
[62] Gorantla VS, Prabhune KA, Perez-Abadia G, et al. Composite tissue allotransplantation in chimeric hosts: part I. Prevention of graft-versus-host disease. Transplantation 2003;75: 922–32.
[63] Prabhune KA, Gorantla VS, Perez-Abadia G, et al. Composite tissue allotransplantation in chimeric hosts part II. A clinically relevant protocol to induce tolerance in a rat model. Transplantation 2003;76:1548–55.
[64] Perez-Abadia G, Laurentin-Perez L, Gorantla VS, et al. Low-dose immunosuppression in a rat hind-limb transplantation model. Transpl Int 2003;16:835–42.
[65] Brouha P, Perez-Abadia G, Francois C, et al. Lymphadenctomy prior to rat hind limb allotransplantation prevents graft-versus-host disease in chimeric hosts. Transpl Int 2004;17: 341–50.
[66] Francois CG, Brouha PCR, Laurentin-Perez LA, et al. Vascularized lymph node transplantation induces graft-versus-host-disease in chimeric hosts. Transplantation 2006;81(10):1435–41.
[67] Ren X, Shirbacheh M, Ustuner E, et al. Radial forelimb osteomyocutaneous flap as a preclinical composite tissue allograft (CTA) model in swine. Microsurgery 2000;20:143–9.
[68] Ustuner ET, Majzoub RK, Ren X, et al. Swine composite tissue allotransplant model for preclinical hand transplant studies. Microsurgery 2000;20:400–6.
[69] Shirbacheh M, Jones J, Breidenbach W, et al. The feasibility of human hand transplantation. Presented at the Seventh IFSSH Congress. Vancouver (Canada), May 24–28, 1998.
[70] Jones JW Jr, Ustuner ET, Zdichavsky M, et al. Long-term survival of an extremity composite tissue allograft with FK506-mycophenolate mofetil therapy. Surgery 1999;126:384–8.
[71] Dubernard JM, Owen E, Herzberg G, et al. Human hand allograft: report on first 6 months. Lancet 1999;353:1315–20.
[72] Jones JW, Gruber SA, Barker JH, et al. Successful hand transplantation. One-year follow-up. Louisville hand transplant team. N Engl J Med 2000; 343:468–73.
[73] Francois CG, Breidenbach WC, Maldonado C, et al. Hand transplantation: comparisons and observations of the first four clinical cases. Microsurgery 2000;20:360–71.
[74] Kanitakis J, Jullien D, Petruzzo P, et al. Clinicopathologic features of graft rejection of the first human hand allograft. Transplantation 2003; 76:688–93.
[75] Lanzetta M, Petruzzo P, Margreiter R, et al. The international registry on hand and composite

tissue transplantation. Transplantation 2005; 79:1210–4.
[76] Altman L. The doctor's world; doctors who transplanted hand ponder their surprising patient 2006. Available at: http://query.nytimes.com/gst/fullpage.html?res=9A03E0D61E38F935A35753C1A96E958260&sec=health. Accessed May 3, 2006.
[77] Kanitakis J, Petruzzo P, Jullien D, et al. Pathological score for the evaluation of allograft rejection in human hand (composite tissue) allotransplantation. Eur J Dermatol 2005;15:235–8.
[78] Lanzetta M, Ayrout C, Gal A, et al. Experimental limb transplantation, part II: excellent return of function and indefinite survival after withdrawal of immunosuppression. Transplant Proc 2004; 36:675–9.
[79] Lee WP, Yaremchuk MJ, Pan YC, et al. Relative antigenicity of components of a vascularized limb allograft. Plast Reconstr Surg 1991;87: 401–11.
[80] Rush D, Nickerson P, Gough J, et al. Beneficial effects of treatment of early subclinical rejection: a randomized study. J Am Soc Nephrol 1998;9:2129–34.
[81] Miyagi M, Ishikawa Y, Mizuiri S, et al. Significance of subclinical rejection in early renal allograft biopsies for chronic allograft dysfunction. Clin Transplant 2005;19:456–65.
[82] Shishido S, Asanuma H, Nakai H, et al. The impact of repeated subclinical acute rejection on the progression of chronic allograft nephropathy. J Am Soc Nephrol 2003;14: 1046–52.
[83] Waaga AM, Gasser M, Laskowski I, et al. Mechanisms of chronic rejection. Curr Opin Immunol 2000;12:517–21.
[84] Matas AJ, Humar A, Payne WD, et al. Decreased acute rejection in kidney transplant recipients is associated with decreased chronic rejection. Ann Surg 1999;230:493–8 [discussion: 498–500].
[85] Tufveson G, Johnsson C. Chronic allograft dysfunction—chronic rejection revisited. Transplantation 2000;70:411–2.
[86] Kanitakis J, Jullien D, Petruzzo P, et al. Immunohistologic studies of the skin of human hand allografts: our experience with two patients. Transplant Proc 2001;33:1722.
[87] Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. N Engl J Med 2003;349:2326–33.
[88] Pascual M, Theruvath T, Kawai T, et al. Strategies to improve long-term outcomes after renal transplantation. N Engl J Med 2002;346:580–90.
[89] Vasilic D, Alloway RR, Barker JH. Risk assessment of immunosuppressive therapy in facial transplantation. Plast Reconstr Surg 2006, in press.
[90] The UK Face Transplant Information Website; 2006. Available at: http://www.facialtransplantation.org.uk/content/info2.asp. Accessed March 15, 2006.
[91] Dougherty H. Burns girl to have first face transplant; 2003. Available at: http://www.thisislondon.com/news/articles/3609267?source=Evening%20Standard. Acessed April 26, 2006.
[92] Lena Marie Murphy: apology; 2003. Available at: http://www.unison.ie/irish_independent/stories.php3?ca=9&si=928546&issue_id=8841. Accessed April 26, 2006.
[93] Barker J. Naked science—face of the future, public debate on the feasibility of face transplantation. In: Public debate on the feasibility of face transplantation. London Science Museum, Dana Center. London, UK, November 19, 2003, 2003.
[94] Morris P, Bradley A, Doyal L, et-al. Facial transplantation: working party report; 2003. Available at: http://www.rcseng.ac.uk/rcseng/content/publications/docs/facial_transplantation.html. Accessed April 30, 2006.
[95] Jiang HQ, Wang Y, Hu XB, et al. Composite tissue allograft transplantation of cephalocervical skin flap and two ears. Plast Reconstr Surg 2005;115:31e–5e [discussion: 36e–7e].
[96] China's 1st face transplant successful; 2006. Available at: http://news.xinhuanet.com/english/2006-04/14/content_4425653.htm. Accessed April 15, 2006.
[97] Devauchelle B, Badet L, Lengele B, et al. First human face allograft: early report. Lancet 2006;368: 203–9.
[98] The first facial transplant. Lancet 2005;366: 1984.
[99] Butler PE, Hettiaratchy S, Clarke A. Facial transplantation: a new gold standard in facial reconstruction? J Plast Reconstr Aesthet Surg 2006; 59:211–2.
[100] McCabe S, Rodocker G, Julliard K, et al. Using decision analysis to aid in the introduction of upper extremity transplantation. Transplant Proc 1998;30:2783–6.
[101] Wiggins OP, Barker JH, Martinez S, et al. On the ethics of facial transplantation research. Am J Bioeth 2004;4:1–12.
[102] Moore FD. Three ethical revolutions: ancient assumptions remodeled under pressure of transplantation. Transplant Proc 1988;20:1061–7.
[103] Moore FD. The desperate case: CARE (costs, applicability, research, ethics). JAMA 1989;261: 1483–4.
[104] Farrer R. Psychological considerations in face transplantation. International Journal of Surgery 2004;2:77–8.
[105] Haughton RP. Ethical considerations in face transplantation. International Journal of Surgery 2004;2:79–81.
[106] Summerton I, Agha R. Societal considerations in face transplantation. International Journal of Surgery 2004;2:82–83.
[107] Thorburn G, Hettiaratchy S, Ashcroft R, et al. Patient selection for facial transplantation III: ethical considerations. International Journal of Surgery 2004;2:118–119.

[108] Clarke A, Butler PE. Patient selection for facial transplantation II: psychological considerations. International Journal of Surgery 2004;2: 117–118.
[109] Strong C. Should we be putting a good face on facial transplantation? Am J Bioeth 2004;4: 13–4 [discussion: W23–31].
[110] Petit F, Paraskevas A, Lantieri L. A surgeons' perspective on the ethics of face transplantation. Am J Bioeth 2004;4:14–6 [discussion: W23–31].
[111] Butler PE, Clarke A, Ashcroft RE. Face transplantation: when and for whom? Am J Bioeth 2004; 4:16–7 [discussion: W23–31].
[112] Caplan A. Facing ourselves. Am J Bioeth 2004;4: 18–20 [discussion: W23–31].
[113] Agich GJ, Siemionow M. Facing the ethical questions in facial transplantation. Am J Bioeth 2004;4:25–7 [discussion: W23–31].
[114] Morreim EH. About face: downplaying the role of the press in facial transplantation research. Am J Bioeth 2004;4:27–9 [discussion: W23–31].
[115] Baylis F. A face is not just like a hand: pace Barker. Am J Bioeth 2004;4:30–2 [discussion: W23–31].
[116] Robertson JA. Face transplants: enriching the debate. Am J Bioeth 2004;4:32–3 [discussion: W23–31].
[117] Maschke KJ, Trump E. Facial transplantation research: a need for additional deliberation. Am J Bioeth 2004;4:33–5 [discussion: W23–31].
[118] Ankeny RA, Kerridge I. On not taking objective risk assessments at face value. Am J Bioeth 2004;4:35–7 [discussion: W23–31].
[119] Goering S. Facing the consequences of facial transplantation: individual choices, social effects. Am J Bioeth 2004;4:37–9 [discussion: W23–31].
[120] Miles SH. Medical ethicists, human curiosities, and the new media midway. Am J Bioeth 2004;4:39–43.
[121] Chambers T. How to do things with AJOB: the case of facial transplantation. Am J Bioeth 2004;4:20–1.
[122] Cunningham M, Barker J. Response to R. Farrer. Psychological considerations in face transplantation. International Journal of Surgery 2004;2:78–79.
[123] Wiggins O, Barker J. Response to P Haughton, ethical considerations of facial transplantation research. International Journal of Surgery 2004;2: 81–82.
[124] Furr L, Barker J. Response to I. Summerton and R. Agha, sociological considerations in face transplantation. International Journal of Surgery 2004;2:83.
[125] Cunningham M, Barker J. Response to A. Clarke and P.E.M. Butler, patient selection for facial transplantation II: psychological considerations. International Journal of Surgery 2004;2:117–118.
[126] Wiggins O, Barker J. Response to G. Thorburn, S. Hettiaratchy, R. Ashcroft, and P.E.M. Butler patient selection for facial transplantation III: ethical considerations. International Journal of Surgery 2004;2:119.
[127] Banis J, Barker J, Cunningham M, et al. Response to selected commentaries on the AJOB target article "on the ethics of facial transplantation research". Am J Bioeth 2004;4: W23–31.
[128] Barker J, Hewitt C, Breidenbach W. [Invited Editors]. Proceedings of the 2nd International Symposium on Composite Tissue Allotranplantation: special issue. Microsurgery 2000;20.
[129] Barker J, Francois C, Frank J, et al. Composite tissue allotransplantation (CTA): present state and future outlook. Transplantation 2002;73: 832–5.
[130] Gorantla V, Maldonado C, Frank J, et al. Composite tissue allotransplantation (CTA): current status and future insights. Eur J Trauma 2001;7: 267–74.
[131] Gander B, Brown CS, Vasilic D, et al. Composite tissue allotransplantation of the hand and face: a new frontier in transplant and reconstructive surgery. Transplant International 2006; 19:868.
[132] Brown CS, Gander B, Cunningham M, et al. Ethical considerations in face transplantation. International Journal of Surgery, in press.
[133] Banis J, Brouha P, Majzoub R, et al. How much risk are individuals willing to accept to receive composite tissue allotransplantation reconstructive procedures? Presented at the Annual Meeting of the American Association of Plastic Surgery. Seattle (WA), April 2002.
[134] Storey BB, Vasilic D, Cunningham MR, et al. Investigation of risk acceptance in hand transplantation. Presented at the 91st Annual Clinical Congress of American College of Surgeon. San Francisco, October 16–20, 2005.
[135] First International Symposium on Composite Tissue Allotransplantation. Louisville (KY), November 19–20, 1997.
[136] Second International Symposium on Composite Tissue Allotransplantation. Louisville (KY), May 18-19, 2000.
[137] Cunningham M, Majzoub R, Brouha PCR, et al. Risk acceptance in composite tissue allotransplantation reconstructive procedures. Instrument design and validation. European Journal of Trauma 2004;30:12–6.
[138] Brouha P, Naidu D, Cunningham M, et al. Risk acceptance in composite-tissue allotransplantation reconstructive procedures. Microsurgery 2006;26:144–9.
[139] Majzoub RK, Cunningham M, Grossi F, et al. Investigation of risk acceptance in hand transplantation. J Hand Surg [Am] 2006;31:295–302.
[140] Reynolds CC, Martinez SA, Furr A, et al. Risk acceptance in laryngeal transplantation. Laryngoscope 2006;116:1770–5.

[141] Barker JH, Furr A, Cunningham M, et al. Investigation of risk acceptance in facial transplantation. Plast Reconstr Surg 2006;118:663–70.
[142] Working group-Comité Consultatif National d'Ethique (CCNE): composite tissue allotransplantation of the face (Full or Partial facial transplant). 2004. Available at: http://www.ccne-ethique.fr/english/start.htm. Accessed April 30, 2006.
[143] Okie S. Facial transplantation: brave new face. N Engl J Med 2006;354:889–94.
[144] Position of the American Society for Reconstructive Microsurgery on Facial Transplantation. 2006. Available at: http://www.microsurg.org/asrmFTP.pdf. Accessed March 15, 2005.
[145] Facial transplantation ASRM/ASPS guiding principles. 2006. Available at: http://www.microsurg.org/ftGuidelines.pdf. Accessed November 10, 2006.
[146] The United States position: position paper of the American Society for Reconstructive Microsurgery on Facial Transplantation. South Med J 2006;99:430.
[147] Hui-qing J, Xin-bao H, You-sheng L, et-al. Allograft allotransplantation with composite tissue of two ears and skin of head and neck: a report of one case. Chinese Journal of Plastic Surgery 2003;19:416–419.
[148] Olesen A. Chinese face transplant patient healing. 2006. Available at: http://news.yahoo.com/s/ap/20060425/ap_on_re_as/china_face_transplant_4. Accessed May 6, 2006.
[149] Doctors: Chinese face transplant patient doing well. 2006. Available at: http://www.foxnews.com/story/0. Accessed May 6, 2006.
[150] Chinese face op man 'doing well'; 2006. Available at: http://news.bbc.co.uk/1/hi/world/asia-pacific/4915290.stm. Accessed May 6, 2006.
[151] Anonymous. Hand transplanted from cadaver is reamputated. Med Trib Med News 1964;5:23.
[152] Hovius SE, Stevens HP, Van Nierop PW, et al. Replantation of the radial side of the hand in the rhesus monkey: anatomical and functional aspects. A preliminary study to composite tissue allografting. J Hand Surg [Br] 1992;17:651–6.
[153] Thomas A, Obed V, Murarka A, et al. Total face and scalp replantation. Plast Reconstr Surg 1998;102:2085–7.
[154] How to replace a face; 2004. Available at: http://www.newscientist.com/article.ns?id=dn5042. Accessed November 10, 2006
[155] Cheng K, Zhou S, Jiang K, et al. Microsurgical replantation of the avulsed scalp: report of 20 cases. Plast Reconstr Surg 1996;97:1099–106. [discussion: 1107].
[156] McDowell N. Surgeons struggle with ethical nightmare of face transplants. Nature 2002;420:449.
[157] Hettiaratchy S, Butler PE. Face transplantation—fantasy or the future? Lancet 2002;360:5–6.
[158] Eduardo Bermu Dez L, Santamaria A, Romero T, et al. Experimental model of facial transplant. Plast Reconstr Surg 2002;110:1374–5.
[159] Talking science—the 24 hour museum goes to the Dana center; 2006. Available at: http://www.24hourmuseum.org.uk/nwh_gfx_en/ART18716.html. Accessed March 17, 2006.
[160] Meningaud JP. Facial grafts: the ethical issue. Rev Stomatol Chir Maxillofac 2003;104:131–2 [German].
[161] Kmietowicz Z. Face transplants should not be done without more research. BMJ 2003;327:1184.
[162] Hull AM, Lowe T, Devlin M, et al. Psychological consequences of maxillofacial trauma: a preliminary study. Br J Oral Maxillofac Surg 2003;41:317–22.
[163] Siemionow M, Gozel-Ulusal B, Engin Ulusal A, et al. Functional tolerance following face transplantation in the rat. Transplantation 2003;75:1607–9.
[164] Ulusal BG, Ulusal AE, Ozmen S, et al. A new composite facial and scalp transplantation model in rats. Plast Reconstr Surg 2003;112:1302–11.
[165] Wilhelmi BJ, Kang RH, Movassaghi K, et al. First successful replantation of face and scalp with single-artery repair: model for face and scalp transplantation. Ann Plast Surg 2003;50:535–40.
[166] Trachtman H. Facing the truth: a response to "on the ethics of facial transplantation research" by Wiggins et al. Am J Bioeth 2004;4:W33–W34.
[167] Morris PJ, Bradley JA, Doyal L, et al. Facial transplantation: a working party report from the Royal College of Surgeons of England. Transplantation 2004;77:330–8.
[168] Klotzko A. About a face. Prospect 2004;94:14–5.
[169] Bosch X. Surgeon denied ethics approval for face transplantation. Lancet 2004;363:871.
[170] Check E. Surgeons seek go-ahead to perform first face transplant. Nature 2004;431:389.
[171] [No authors listed]. Full or partial face transplants. Bull Med Ethics 2004;(202):9–11.
[172] Morris PJ, Monaco AP. Facial transplantation: is the time right? Transplantation 2004;77:329.
[173] Huxtable R, Woodley J. Gaining face or losing face? Framing the debate on face transplants. Bioethics 2005;19:505–22.
[174] Hettiaratchy S, Randolph MA, Petit F, et al. Composite tissue allotransplantation—a new era in plastic surgery? Br J Plast Surg 2004;57:381–91.
[175] Petit F, Paraskevas A, Minns AB, et al. Face transplantation: where do we stand? Plast Reconstr Surg 2004;113:1429–33.
[176] Rumsey N, Clarke A, White P, et al. Altered body image: appearance-related concerns of people with visible disfigurement. J Adv Nurs 2004;48:443–53.
[177] Siemionow M, Ozmen S, Demir Y. Prospects for facial allograft transplantation in humans. Plast Reconstr Surg 2004;113:1421–8.

[178] Petit F, Minns AB, Nazzal JA, et al. Prolongation of skin allograft survival after neonatal injection of donor bone marrow and epidermal cells. Plast Reconstr Surg 2004;113:270–6.
[179] Demir Y, Ozmen S, Klimczak A, et al. Tolerance induction in composite facial allograft transplantation in the rat model. Plast Reconstr Surg 2004;114:1790–801.
[180] Wendt JR, Ulich T, Rao PN. Long-term survival of human skin allografts in patients with immunosuppression. Plast Reconstr Surg 2004; 113:1347–54.
[181] Kelly M, Butler P. Patient selection for facial transplantation I: anatomical and surgical considerations. International Journal of Surgery 2004;2:114–116.
[182] Banis J, Barker J. Response to: M. Kelly and P.E.M. Butler, patient selection for facial transplantation I: anatomical and surgical considerations. International Journal of Surgery 2004;2: 115–116.
[183] Nau JY. History of the first partial face transplant. Rev Med Suisse 2005;1:3002 [Article in French].
[184] Clark J. Face transplants technically possible, but "very hazardous". CMAJ 2004;170:323.
[185] Clark PA. Face transplantation: a medical perspective. Med Sci Monit 2005;11:RA1–6.
[186] Clark PA. Face transplantation: part II—an ethical perspective. Med Sci Monit 2005;11: RA41–7.
[187] Martin J. Patient satisfaction, measure of the ethical character of medical acts? About the face transplant in Amiens. Rev Med Suisse 2005;1:3003 [Article in French].
[188] Butler PE, Clarke A, Hettiaratchy S. Facial transplantation. BMJ 2005;331:1349–50.
[189] Hartman RG. Face value: challenges of transplant technology. Am J Law Med 2005;31:7–46.
[190] Agich GJ, Siemionow M. Until they have faces: the ethics of facial allograft transplantation. J Med Ethics 2005;31:707–9.
[191] Siemionow M, Agaoglu G. Allotransplantation of the face: how close are we? Clin Plast Surg 2005;32:401–9, vii.
[192] Siemionow MZ, Demir Y, Sari A, et al. Facial tissue allograft transplantation. Transplant Proc 2005;37:201–4.
[193] Martin J. Face transplantation: psychological, social, ethical and legal considerations. Rev Med Suisse 2005;1:583–4 [Article in French].
[194] Siemionow M, Demir Y, Mukherjee A, et al. Development and maintenance of donor-specific chimerism in semi-allogenic and fully major histocompatibility complex mismatched facial allograft transplants. Transplantation 2005;79: 558–67.
[195] Horch RE, Jeschke MG, Spilker G, et al. Treatment of second degree facial burns with allografts —preliminary results. Burns 2005;31:597–602.
[196] Unal S, Agaoglu G, Zins J, et al. New surgical approach in facial transplantation extends survival of allograft recipients. Ann Plast Surg 2005;55:297–303.
[197] Clarke A, Butler PE. Facial transplantation: adding to the reconstructive options after severe facial injury and disease. Expert Opin Biol Ther 2005;5:1539–46.
[198] Spurgeon B. Surgeons pleased with patient's progress after face transplant. BMJ 2005;331: 1359.
[199] UK full face transplant search on 2005. Available at: http://news.bbc.co.uk/1/hi/health/4533278.stm. Accessed June 5, 2006.
[200] Nau JY. Story of the first partial face transplant. Rev Med Suisse 2006;2:76 [Article in French].
[201] Furr A, Wiggins O, Cunningham M, et al. Psychosocial implications of disfigurement and the future of human face transplantation. Plast Reconstr Surg, in press.
[202] Clarke A, Simmons J, White P, et al. Attitudes to face transplantation: results of a public engagement exercise at the royal society summer science exhibition. J Burn Care Res 2006;27: 394–8.
[203] Bermudez L. Face transplant: is it worth it? Plast Reconstr Surg 2006;117:1891–6.
[204] Hamdy RC. Face transplantation: a brave or maverick surgery? South Med J 2006;99:410–1.
[205] Daly CC. Saving face. South Med J 2006;99: 412–3.
[206] Peled ZM, Pribaz JJ. Face transplantation: the view from Harvard Medical School. South Med J 2006;99:414–6.
[207] Walton RL, Levin LS. Face transplantation: the view from Duke university and the university of Chicago. South Med J 2006;99:417–8.
[208] Shack B. Face transplantation: the view from Vanderbilt University. South Med J 2006;99: 419–20.
[209] Lantier LA. Face transplantation: the view from Paris, France. South Med J 2006;99:421–3.
[210] Wigmore SJ. Face transplantation: the view from Birmingham, England. South Med J 2006;99: 424–6.
[211] Hutchison I. Face transplants: is the genie out of the bottle? South Med J 2006;99:427–9.
[212] [No author listed]. The English position: position paper of the Royal College of Surgeons of England. South Med J 2006;99:431.
[213] The French position: Comite Consultatif National d'Ethique pour les sciences de la vie et de la sante: "composite tissue allograftransplantation of the face (total or partial graft)". South Med J 2006;99:432–3.
[214] Rohrich RJ, Longaker MT, Cunningham B. On the ethics of composite tissue allotransplantation (facial transplantation). Plast Reconstr Surg 2006;117:2071–3.
[215] Powell T. Face transplant: real and imagined ethical challenges. J Law Med Ethics 2006;34(114): 111–5.
[216] Hettiaratchy S, Butler PE. Tolerance induction in composite facial allograft transplantation in

the rat model. Plast Reconstr Surg 2006;117: 1043–4. [author reply: 1044–5].
[217] Petit F, Lantieri L, Randolph MA, et al. Future research in immunology for composite tissue allotransplantation. Ann Chir Plast Esthet 2006; 51:11–7 [Article in French].
[218] Siemionow M, Unal S, Agaoglu G, et al. A cadaver study in preparation for facial allograft transplantation in humans: part I. What are alternative sources for total facial defect coverage? Plast Reconstr Surg 2006;117:864–72 [discussion: 873].
[219] Siemionow M, Agaoglu G, Unal S. A cadaver study in preparation for facial allograft transplantation in humans: part II. Mock facial transplantation. Plast Reconstr Surg 2006;117: 876–85 [discussion: 886–8].
[220] Simpson P, Batchelor A. Face transplants. Lancet 2006;367:469.
[221] Toure G, Meningaud JP, Bertrand JC, et al. Facial transplantation: a comprehensive review of the literature. J Oral Maxillofac Surg 2006;64:789–93.
[222] Petit F. The new face of reconstructive surgery. Presse Med 2006;35:7–8 [Article in French].