The face and scalp define functionally and aesthetically important units. Traumatic deformities of the head and neck region resulting from burn injuries, gunshot wounds, or ablative tumor surgeries may be presented as a single defect, such as of the skin, the subcutaneous tissue, or the muscle, or as a combination defect involving all three units. The optimal reconstruction of these specialized units is difficult to achieve. Sometimes, a major part of the face along with the entire composite subunit, such as the ear or the nose, may be involved.1-3 Extensive scalp loss due to burn or avulsion injury is another deforming and psychologically debilitating condition that presents a major reconstructive challenge.

Prefabrication of flaps is widely used for coverage of different facial, neck, and scalp defects.4-6,17,18 Prefabricated flaps can provide a sufficient amount of tissue for lining and support in limited-size defects, but the disadvantages are the color and texture mismatch and the need for additional, often multiple, revision procedures.17

Expanded skin flaps are frequently used in facial reconstruction to provide tissue that is identical in texture and color as well as in sensibility.19,20 This technique offers a reasonable alternative to the standard technique of skin grafting and distant flap transfer, and in many cases it may yield better aesthetic and functional results.19

When there is a lack of adjacent tissue available during reconstruction of extensive facial/scalp defects, microsurgical free tissue transfers may be indicated.10,21 Free flaps are valuable sources of tissue for coverage of composite facial defects, for oral and nasal linings, and for filling of defects, when the bulk of tissue is needed for reconstruction of defects following
ablative procedures. The disadvantage is the visible evidence of skin color and tissue texture mismatch, which is a limiting factor in obtaining an acceptable aesthetic reconstruction.

**Replantation of the Facial and Scalp Components**

Partial or total face and scalp loss secondary to avulsion injury represents a significant cosmetic and emotional disfigurement and operative challenge. Replantation of the avulsed parts was attempted even when subunits of the facial tissue were partially damaged, and successful facial flap replantation gives reasonable functional and aesthetic results.22–24

**Facial Reconstruction Using Composite Tissue Allotransplantation**

Transplantation of composite tissue allografts, such as the human hand, larynx, and knee joint, has become a clinical reality.25–27 Currently more than 20 successful hand transplants have been reported from different centers all over the world.25,28 Success in composite tissue allograft transplantation has created an option for routine applicability of these highly antigenic tissue transplants, including vascularized skin. Recent press announcements and media debate on the applicability of allogeneic face transplantation have gained a lot of public attention. It has been suggested that face allotransplantation could be a reconstructive alternative for patients with complex facial deformities that cannot be corrected by application of currently available reconstructive procedures.29 The immunological and social aspects of this new approach to facial reconstruction should be discussed further before appropriate candidates are selected.

Our research interest during the past 15 years concentrated on the tolerance-inducing strategies for composite tissue transplants.30–34 We were able to induce tolerance under a 7-day protocol of combined αβ-T-cell receptor monoclonal antibody and cyclosporine therapy in the rat hindlimb transplantation model. The natural progression of the composite limb allograft application could be the composite face/scalp allotransplantation.

Our attempt was to consider the best reconstructive options for face and scalp coverage, with the hope that allogeneic transplantation would provide the best aesthetic and functional results. Therefore, on the basis of our previous experience with composite allografts, we have introduced a composite face and scalp transplantation model in rats to investigate its technical feasibility, immunological considerations, and potential for future clinical applicability.30

**Experimental Model**

Combined total face/scalp allograft transplantations were performed between Lewis (LEW, RT1) and Lewis–Brown Norway (LBN RT1) rats.35 The facial/scalp flap was harvested as a single unit and included both ears. The recipient’s periocular and perioral regions were preserved to prevent the development of functional deficiencies, which would make animal feeding and breathing difficult. In the donor, both the common carotid arteries and the jugular veins were used as the vascular pedicles. The recipient’s face and scalp were excised as a full-thickness skin graft to preserve the facial nerve and muscles. In the recipient, either the common or the external carotid arteries and the anterior facial veins were used for anastomosis.

**Immunosuppressive Protocol**

No recipient conditioning was applied, and monotherapy with cyclosporine was used for immunosuppression to prevent allograft rejection. Cyclosporine (16 mg per day) was initiated on the day of surgery and was tapered by 50 percent each week to 2 mg/kg over a 4-week period. After 4 weeks, cyclosporine monotherapy was maintained at this level, which led to the long-term survival of the composite face/scalp flaps (Fig. 1). Our resulting successful maintenance of the face/scalp allograft transplants for 330 days using a single-agent immunosuppressive therapy protocol without the need for recipient conditioning is encouraging, and similar approaches may be applicable in the future for clinical consideration of this challenging procedure.

**Surgical Considerations for Facial Allotransplantation in Humans**

The human face is an aesthetic and functionally dynamic organ. Most of the conventional reconstructive techniques result in a “mask-like” appearance, quite often without facial movement and recognition of patient identity. In the search for new techniques and alternatives for facial reconstruction, allograft transplantation in the form of isolated subunits or a single integrated face/scalp unit may be a
promising alternative. Transplantation of the “all-missing subunits” in one surgical procedure seems to be the most challenging option, but it is the only logical option for achieving the best functional and aesthetic results.

The Model

Compared with the experimental animal models, transplantation of the face and scalp in humans should be technically less challenging due to the large size of the anatomical structures. In our experimental studies using a rat model, the attention was focused on the technical success and long-term survival of the face allograft transplants. In humans, in addition to satisfactory aesthetic results, the optimal functional outcome should also be achieved with the ability to restore facial expression and functioning facial muscles. After burn injury, the facial muscles usually remain intact beneath the scarred tissue. The mask-like appearance in these patients is most likely due to the hard, nonpliable scar covering the underlying facial muscles. Removal of damaged skin followed by transfer of the composite facial skin allograft could release contracture of the underlying muscles, which in turn would permit return of facial function. Thus, the facial skin allograft should be thin and pliable to allow for expression of facial animation and prevention of a mask-like appearance. Moreover, it may be technically possible to transplant facial muscles...
as a part of the composite allograft, provided that the donor’s facial nerve is included. Appropriate donor and recipient nerve cooptation following nerve regeneration may provide restoration of a functional face, since it is possible to perform neurorrhaphy among the infraorbital, mental, facial, supraorbital, and supratrochlear nerves. In humans, the vascular anatomy is consistent, there are rich vascular plexuses in the subcutaneous tissue, and the anatomic territories are linked by the choke vessels. Therefore, it is possible to elevate the face, the scalp, or both as one composite flap based bilaterally on the external carotid arteries and jugular veins. In the recipient, suitable vessels for microsurgical anastomosis would be the external carotid artery and its branches, the jugular vein, the facial artery, and the facial vein.

**Technical Considerations**

When harvesting the composite facial allograft, the critical ischemia time will be longer compared with the time for solid organ procurement. Harvesting the entire face/scalp flap requires paying meticulous attention to detail to preserve the vascular supply and territories. The facial flap procurement will be based on two vascular pedicles and take a much longer time compared with human hand harvesting, which is technically less challenging and has already been applied clinically in composite tissue allotransplantation.

One of the most important issues that should be considered is the potential risk of vascular failure and the risk of rejection by the host immune system. The risk of acute flap failure due to the vascular problems can be minimized by reducing ischemia time and applying meticulous microsurgical techniques. The secondary “rescue procedures” have to be outlined. If no-reflow failure occurs following transplantation, reconstruction of the face will become challenging for both the patient and the physician. One option would be to perform microsurgical anastomoses of the facial flap before removal of the scarred skin graft from the recipient. Once perfusion of the facial allograft is established, resection of the scarred tissue can be performed, followed by final insetting of the facial flap. During the same procedure, autologous skin can be harvested as a whole unit from the recipient and used for grafting if acute flap failure occurs. This choice, however, would not be applicable for late flap failure of vascular or immunologic origin. Solid organ transplantation protocols are well established and routinely used in clinical practice, so failure rates are well documented. Graft survival at 6 months has been reported to be 95.55 percent for kidney transplants and 87.0 percent for liver transplants. At 3-year follow-up, this ratio decreases to 89.6 percent and 75.6 percent, respectively. One third of the allografts may fail at 10-year follow-up. The long-term outcome in composite tissue allograft transplantation is not certain and cannot be quantified because there are a limited number of transplants and the longest follow-up period is 5 years. The functional results of hand allograft transplants are promising, but we cannot predict when rejection may occur and if functional outcome will decline in cases of chronic rejection. Only one out of 20 hand transplantations was rejected secondary to a patient’s psychological problems and noncompliance. All other transplanted hands went through shorter or longer episodes of rejection, which were managed by adjustment of immunosuppressive protocols. The risk of rejection should be discussed in detail with the patient and the transplant team before transplantation. Clinical assessment of donor-site availability for the “rescue procedures,” such as skin grafting and free tissue transfers, should be outlined. The possibility of using prosthetic material for coverage should be considered the last option.

**Immunosuppressive Protocol**

Another important issue when considering transplantation of the face/scalp allograft in humans is the need for life-long immunosuppression. Allotransplantation of solid organs such as the kidney, liver, heart, and lungs is essential for life, so the side effects of immunosuppressive therapy are accepted by the patient and by society. Transplantation of composite tissue allografts, such as the human hand, may offer better quality-of-life but is not essential for sustaining life. It is difficult to quantify the benefits of composite tissue allograft transplantation or the risk of life-long immunosuppression. The decision to perform composite tissue allograft transplantation should be individualized on a case-by-case basis based on the type of composite tissue to be transplanted. The side effects of immunosuppressive agents currently used for solid organ or composite tissue allograft transplantations affect different organs and systems. The cal-
cineurin inhibitors (cyclosporine and tacrolimus) often used during induction and maintenance therapy target renal and hepatic function. Neurotoxic effects and posttransplant diabetes occur more frequently with tacrolimus, whereas the rates of hypercholesterolemia and the risk of hypertension are lower compared with cyclosporine. Tacrolimus has been shown to promote nerve regeneration in experimental studies, so this agent can be preferred to cyclosporine for composite tissue transplantation, where nerve regeneration will be an important factor for functional outcome, unlike in solid organ transplantation. Glucocorticoids, often-used immunosuppressive agents, showed significant systemic toxic effects with higher doses. These systemic side effects can be diminished by tapering the dose during maintenance therapy. However, the use of glucocorticoids in composite tissue transplantations can negatively affect wound healing, such as on skin of the hand; this is less important following solid organ transplantation, since the organ can function even if wound healing is delayed. Other risks during immunosuppressive therapy include the development of opportunistic infections and malignancy. Immunosuppression-related complications can be prevented by careful monitoring and early medical intervention. Opportunistic viral and fungal infections that developed after human hand transplantation were managed by appropriate treatment protocols without major complications. Prevention of serious immunosuppressant side effects may be maintained by protocol adjustments. This was done following laryngeal transplantation in which cyclosporine, which was used initially, was replaced with tacrolimus to control the hypertension associated with nephrotoxicity. In recent years, attention has been focused on induction of immunologic tolerance in transplant recipients to eliminate the need for life-long immunosuppression and to prevent the development of toxic side effects. Bone marrow transplantation, in addition to standard-line protocols, has been investigated. Experimental animal studies showed that donor-specific tolerance can be achieved through development of stable mixed allogeneic chimerism after bone marrow transplantation. Using the vascularized bone marrow transplantation model, we have induced tolerance under a 7-day protocol of cyclosporine and αβ-T-cell receptor antibodies. Another strategy to induce tolerance is blockade of certain costimulatory molecules. Activation of costimulatory molecules such as CD40, CD80, and CD28 is necessary to generate an alloimmune T-cell response. Blockade of these pathways by monoclonal antibodies was shown to prolong allograft acceptance in rodents. Anti-CD3 immunotoxin, a T-cell–depleting agent, was shown to induce functional tolerance and extend renal allograft survival in primates. Humanized, mutagenized anti-CD3 monoclonal antibodies (CAMPATH) have been used in renal transplantation trials and have shown promising results as a tolerance induction strategy for future clinical applications. This new generation of humanized monoclonal antibody offers a new immunosuppressive and tolerance-inducing treatment modality.

Since composite tissue allotransplantations are not life-saving procedures, the side effects of immunosuppressive agents raise a question about the risk-benefit balance of these transplants. Transplantation of the facial allograft, however, is quite distinct from other composite tissue allotransplantations. The face and scalp are the most visible aesthetic units in the body, and severe facial deformity (e.g., secondary to burn injury or mechanical trauma) often leads to serious social and physiological consequences. In the affected patients, the sociopsychological benefits of face allotransplantation may offset the potential side effects of life-long immunosuppression. Currently, transplantation of the face would be a treatment of choice for victims of facial burns and trauma, if life-long immunosuppressive protocols were not necessary and tolerance-inducing strategies were available. It seems quite likely that in the near future standard tolerance-inducing protocols will be introduced, opening a new era for all composite tissue allotransplantations.

The following are surgical points that should be considered for facial allotransplantation in humans:

- In addition to the tissue antigen match, the skin color, texture, age, and sex of the patient should also be considered during selection of the proper donor. This may significantly limit the donor’s availability and extend the length of the donor selection process.
- If coverage of a bony defect will be needed in addition to soft-tissue coverage, a one-stage reconstruction can be achieved by incorporating structural components such
as bone and muscle into the facial allo-transplantation. This procedure, however, will extend the total harvesting time, the ischemia time, and the entire transplantation procedure.

• Face allotransplantation seems to be an appealing option for patients undergoing post-cancer reconstruction. However, one of the major concerns here is the maintenance of anticancer protocols, which cannot be delayed or compromised by the donor selection process. Moreover, introduction of the immunosuppressive treatment for prevention of face allograft rejection may increase the risk of primary cancer recurrence or may induce secondary malignancies in the already immunocompromised recipient. This issue has to be presented to the patient and discussed by the expert team.

• An important issue pertinent to all transplantation procedures is the possibility of transferring infectious agents such as human immunodeficiency virus, hepatitis C virus, and hepatitis B virus from the donor to the recipient. During routine preparation for the transplantation procedure, most of these agents can be checked by appropriate screening tests. However, some infectious agents (e.g., virions and prions) and some mutant forms may not be detected or predicted at the time of transplantation. These agents should be considered a potential unpredictable risk factor.

**SOCIAL AND PSYCHOLOGICAL CONSIDERATIONS FOR FACE ALLOTRANSPLANTATION IN HUMANS**

Face allograft transplantation from the chosen donor opens a social, ethical, and psychological debate that society, recipients, and recipient and donor families will have to face on a daily basis. The psychological and social consequences of this new procedure can be envisioned, but the final outcome cannot be predicted. Considerations for choosing the proper recipient should be discussed, and considerations for donor selection should be outlined. Finally, the pros and cons of these selection criteria must be discussed by the transplant team.

The outcome of the selection process should be presented to the experts in the medical community, including plastic surgeons, transplant surgeons, immunologists, psychiatrists, psychologists, infectious disease specialists, ethics and bioethics committee members, and legal representatives of the medical community. Appropriate institutional review board protocols should be submitted, discussed, and approved by the leading institutions.

Harvesting of the total face flap from the donor will create a significant defect that may be not acceptable to the donor or the donor’s family. Thus, finding a facial transplant donor will be a much more challenging task compared with the solid organ donation process. Therefore, “reconstructive” options for the facial allograft donor should also be considered.

After the harvesting procedure, repair of the created defect may include coverage of the donor site with a full-thickness skin graft taken from the abdomen, as a single “mask-like” unit. Another, less aesthetically pleasing option would be multiple full-thickness grafts for defect coverage. Finally, synthetic materials and silicone masks, currently commercially available, should be discussed. There is no further need to emphasize that the face and scalp are the most important functional and aesthetic units of the human body. Therefore, the ability to include transplantation of the integral facial components in the routine clinical scenario would revolutionize the field of transplantation and reconstructive surgery. The technical and social considerations of total face allotransplantation outlined above indicate that the best candidates for face allotransplantation would be patients with severe burn injuries and traumatic deformities. The selection of both the donor and the recipient should be well prepared. The technical considerations will be more permissive in humans compared to the experimental models, because the anatomical structures are better defined and nerve cooperation is technically feasible, allowing for reconstruction of the sensate flaps and restoration of muscle function.

**ECONOMIC CONSIDERATIONS FOR FACE ALLOTRANSPLANTATION**

It is anticipated that face allograft transplantation will be a costly procedure. This issue should be taken into consideration when planning transplantation surgery, along with the cost of life-long immunosuppressive drugs. The average cost of organ transplantation is $170,000 for heart transplantation, $55,000 for kidney transplantation, and $95,000 for liver transplantation, according to data from The Cleveland Clinic Foundation transplantation program. The in-hospital cost of the first laryn-
geal allotransplantation was around $150,000. It is well known that the cost of immunosuppressive maintenance therapy ranges from $10,000 to $12,000 per year of the patient’s life. On the basis of these data, we estimate the cost of face allograft transplantation will be similar to that of other composite tissue allograft transplants and will range from $100,000 to $150,000 plus the cost of life-long immunosuppression. Since the cost is high and insurance companies are not currently covering composite tissue allograft transplantation, the question remains, who will pay for this expensive procedure? Would hospitals bear the cost, considering the innovative surgical approach and potential benefits of advertising and public relations awareness? Would some of the patients be willing to contribute to the cost of this procedure? Could grant agencies or private foundations support such a program if it is nationally based? These questions should be raised, discussed, and answered by the public, medical communities, and insurance providers before face allograft transplantation becomes a clinical reality.

There is no doubt that patients and society would greatly benefit from this revolutionary approach, but the question remains, are we ready for such a great psychosociological challenge? Open discussions, a scientific approach, and research on technical and immunological aspects of this new face transplant program should continue. The functional outcome should be a breakthrough rather than a medical and social disaster.

Maria Siemionow, M.D., Ph.D. 
Department of Plastic Surgery, A-60 
The Cleveland Clinic Foundation 
9500 Euclid Avenue 
Cleveland, Ohio 44195 
siemion@ccf.org

REFERENCES
24. James, N. J. Survival of large replanted segment of up-


