Current Concepts and Future Challenges in Facial Transplantation

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KEYWORDS

• Face transplantation • Functional results • Immunotherapy
• Neuropsychology • Indications • Ethics

"The face is always of an Other..." Emmanuel Levinas, philosopher (Ethique et Infini. Paris: Fayard; 1982)

In the writings of ancient Greek philosophy and, more recently, in the texts of leading contemporary thinkers, the face has always embodied the essential expression of humanity. Individual by nature and expressing each single emotion of its owner at any given moment in a unique relationship with the exterior world, the face enjoys an unequalled symbolic value in the midst of a company of animated organs as bearer of the soul. Envisaging transposing the face of one person to another, albeit in order to restore the appearance of a human being, becomes an enterprise that is audacious, provocative, and transgressive. Constrained to the esoteric world of myth and legend until the dawn of the second millenium, such an intervention nevertheless has progressively entered the spheres of mere probability rather than possibility with the advance of science.

When the first facial graft was performed in Amiens, France, on November 27, 2005,[1] this surgical event, which largely surpassed medical boundaries, raised many questions. It did not fail, and rightly so, to launch a society-wide ethical and philosophic debate.[2] Since then three facial allotransplantations (FATs) have been performed, first in Xian, China,[3] then in Paris,[4] and, more recently, in Cleveland, Ohio, in the United States.[5] Today, as emotions subside, a retrospective analysis of the results obtained from those successive clinical experiences enables an initial account of the techniques, results, and cost-benefit balance of FATs.

This article addresses four fundamental issues raised in the medical world by the principle of facial transplantation, even though this procedure has long since passed from the stage of the conceptual virtual world of yesteryear to the surgical reality of today:

- The first issue is technical and concerns the microsurgical feasibility of composite tissue transfers to the face. This opportunity is analyzed from a perspective of interest not only in the static restoration of surfaces and volumes but also in restoring the vectors of facial expression.
- The second issue is biologic and concerns the possibility of medically limiting the rejection of a composite tissue allograft (CTAG), reputedly extremely immunogenic due to its skin cover.
- The third issue is functional and neurophysiologic and raises the question of a possible integration of a facial allograft (FAG) not only in the body scheme of the recipient but also in the day-today life of facing the reality in the mirror and in the gaze of fellow human

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beings. This is precisely the point where essential fears of seeing a massive transfer of the identity of the donor to the recipient, along with the organic transfer of visible nonautologous tissues, come to light. The dread of a major psychologic conflict of personality, therefore, is expected.

- The last issue is ethical and questions the legitimacy of high-risk surgery that mutilates the image of one patient who is about to die in order to pass it to one who, deprived of a face, is about to receive it at the price of the uncertainty of a future existence resulting from the risks engendered by the immunosuppressive treatment and the unknown longevity of the allograft.

Addressing these four cardinal issues and looking beyond current achievements, the author outlines the needs for further research, potential new indications, and future technical challenges concerning new FAGs.

TECHNICAL FEASIBILITY AND JUSTIFICATION OF INDICATIONS FOR FACIAL ALLOGRAFTS

Under the apparent continuity of its form and contours, the face is surgically divided into distinct anatomic units, each of which must, in principle, be the object of a separate reconstruction to be cosmetically perfectly individualized in the rebuilt face. Following this rule, each loss of facial substance limited to a single anatomic unit easily can be repaired with one or several reliable alternative restoration techniques, whose indications, advantages, and disadvantages have been described abundantly. Usually, when only one unit is missing, for example, the nose, lips, eyelids, cheeks, or forehead, it can have its contours, surface, and multitissular architecture elegantly restored with the help of autologous surrounding tissues, with steadfast morphologic results and a satisfactory cosmetic appearance. This is not always the case when a tissue defect is more substantial and concerns several adjacent anatomic units. In spite of the considerable contribution offered, in such circumstances, by microsurgical transfers, several operative procedures are then necessary to restore the bony support of the missing units and to reposition superficially, side by side, the corresponding soft tissues. Despite multiple reinterventions, the results of these daring undertakings are poor, more than often cosmetically imperfect, and nearly always incapable of reviving the dynamics of the lost facial harmony.[6] A face reconstructed in this manner invariably takes on the appearance of a mosaic of juxtaposed cutaneous units, often different in color and texture, separated by multiple scars at wound edges and robbed of the subtle movements required for the oral function and facial expressivity. Precisely because the 3-D multitissular architecture of the face is of unrivalled complexity compared with the rest of the human body, it is justifiable to turn to composite tissue allotransplantation (CTA) when loss of substance extends over several anatomic units and deprives a patient of several cardinal orofacial functions, such as competent feeding, intelligible speech, and spontaneous nonverbal expression. Experts in complex facial reconstruction have recognized the limits of the microsurgical possibilities in the domain of severe disfigurement.[6,7] In the light of these limits, FAT seems more an act of surgical humility than a pretentious action destined to spectacularly demonstrate extreme microsurgical talent. When, despite all its creativity and know-how inherited from peers, the hand of a surgeon considers itself incapable of restoring the genius of nature, is it not better, perhaps, to accept in all humility that only a loan of the genius of nature itself might enable it to further its science and art?

Anatomically, the face rests on rigid skeletal bases and assembles, narrowly schemed under the skin, the orbicular muscular rings that circle the lips and the eyelids, the multidirectional slings of the elevator and depressor muscles organized around the oral cleft, and the gravitational and antigravitational muscles of the eyebrows. Connected by the fibrous sheath of the superficial musculoaponeurotic system that coordinates their movements, each of those muscles acts on distinct adipose cushions that are distributed in cellular subcutaneous tissue, and the dynamic mask thus constituted is supported in various places by retaining ligaments that are responsible for the expressive mimic of the face. The principle of each FAT technique is first to harvest, then to transfer onto the remaining facial structures of the recipient, all those tissue elements, cut to size, without severing them from the skin surface or from the deep mucosal and periosteal planes. The surgical transposition of these structures is technically possible because of the rich vascularization of the face, which consists of several anastomotic arterial and venous networks, distributed in multiple longitudinal or transverse arcades around the oral, nasal, and palpebral clefts, running between the facial, transverse facial, and superficial temporal vessels. Around the orbital region, the main arterial axes branch on terminal segmental branches of the ophthalmic arteries, arising from the internal carotids. The efficiency of functional complement of that vascular network

has been demonstrated clinically by the complete survival of all the soft tissues of the face after traumatic avulsion and microsurgical reimplantation on the segmental branches of the external carotid artery and their neighboring veins.[8]

In the deeper planes, this same network supplies the periosteal plate of the maxillary and mandibular arches, which therefore can be included, by careful dissection, in custom-made allografts. The latter also include, emerging from the mental, infraorbital, and supraorbital foramina (V_3, V_2, and V_1, respectively), the sensitive segmental branches of the trigeminal nerves (V) necessary to restore proprioceptive and epicritical sensitivity to the transplant. Laterally, in the parotid area, the common trunk or the segmental branches of the facial nerves (VII) are harvested depending on the muscle groups required and in the hope of restoring voluntary motricity to the face transplant.

According to these anatomic principles, there are three main segmental FAGs that can be harvested from one or more branches of the external carotid arterial network:

- The lower central FAG (type I) includes harvesting the donor's nose, lips, and chin from the cutaneous surface to the deep mucosa.[1] It is vascularized by the two facial pedicles dissected down to their emergence from the large vessels of the neck and contains all the oral cleft muscles harvested by subperiosteal elevation, from the zygomatic and maxillary bones to the mandibular rim (**Fig. 1**). These muscles are reinnervated by zygomatic, buccal, and mandibular branches of the facial nerves (VII) dissected as separate segmental rami or traced more proximally up to their common origin on the trunk of the facial nerve. The sensitive nerves of the allograft are the mental (V_3) and infraorbital (V_2) nerves exposed at the corresponding bone foramina and lengthened on their proximal course by intraosseous dissection.[1,9] This standard allograft concerns only the soft tissues of the face[1] (type IA). It may be extended laterally to the cheeks and up to the preauricular areas.[4] In the latter case it also contains the parotids and is raised on the external carotid and jugular axes and on the proximal trunk of the two facial nerves.[4] If necessary, it can extend deeper to include the middle part of the mandibular arch to restore the bone support to the chin (type IB; B = bone). In the latter transplant, the mandibular bone segment then is vascularized by the periosteal network of the two submental arteries, which are connected in the area of the mental foramina with the inferior alveolar arteries. The submental vessels, therefore, must be included and left undamaged when the type IB graft is harvested. Consequently, the latter contains an additional skin surface corresponding to the submandibular region next to the hyoid bone.
- The mid-FAG (type II) contains the nose, upper lip, cheeks, and muscles elevating the oral cleft, equally elevated on right and left[3] facial pedicles. Although it can consist of soft tissues only (type IIA), it usually includes the anterior part of the maxillae and zygomatic arches and a variable segment of the anterior palate (type IIB). Its sensitivity is restored by the infraorbital nerves (V_2), and its motor reinnervation relies on the restored continuity of the zygomatic and buccal rami of the facial nerves (VII), if possible along with that of the buccal nerves (V_3) if tonicity to the buccinator muscles is to be restored (see **Fig. 1**). Depending on the extent of the defect to be reconstructed, the allograft may be very wide and on both sides of the midline or, alternatively, unilateral.[3] In some cases, it can be more or less extended downwards, toward the lower portion of the cheek.
- The upper FAG (type III) includes the superficial planes of the forehead, eyelids, and root of the nose and the deeper planes of the frontalis, glabellar, and orbicularis oculi muscles (see **Fig. 1**). It is raised on the two superficial temporal pedicles and on the supraorbital sensitive nerves (V_1). Deep dissection of the allograft around the palpebral sulci must include the preseptal and periosteal anastomotic vascular circle around the orbital rim to include the shunts connecting the intra- and extracranial vascular networks (see **Fig. 1**). Restoration of palpebral blink motricity is delicate but may be mediated by restoring the continuity of the frontal and zygomatic branches of the facial nerves (VII). To date, this segmental transplantation model remains theoretic, because it never has been implemented clinically.

Unlike the three composite transplants (described previously), which are segmental and linked to large functional, neurovascular territories of the face, the total facial skin allograft (type IV) is a purely tegumental transplant designed to

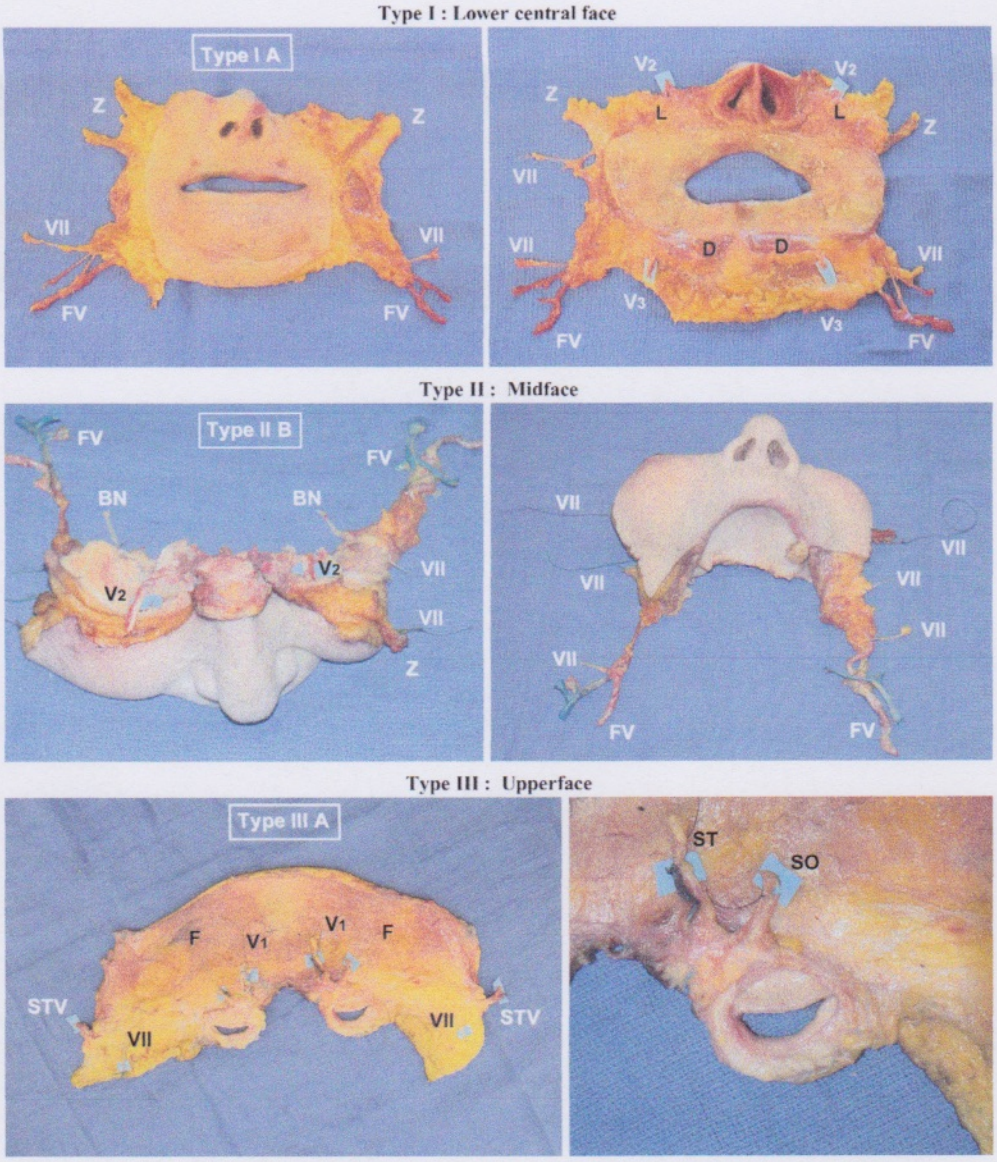

Fig. 1. Surgical classification of segmental facial CTAG. Partial face allografts are functional full-thickness transplants, which include all tissues of the lower (type I), middle (type II), or upper (type III) parts of the facial architecture. They may include soft tissues only (type n-A) or hard and soft tissue together (type n-B; B, bone). All of them are designed to match exactly the facial defect and to include all muscles, motor and sensitive nerves, and lining and to support to restore any missing functions. BN, buccal nerve (V_3); D, depressor muscles of the lower lip; F, frontalis muscles; FV, facial vessels; L, levator muscles of the upper lip; ST, SO, supratrochlear and supraorbital neurovascular pedicles; STV, superficial temporal vessels; V_1, V_2, and V_3, terminal cutaneous branches of ophthalmic, maxillary, and mandibular nerves; VII, facial nerve branches; Z, zygomatic muscles.

restore, in a single segment, the cutaneous cover of the whole facial mask and a variable portion of scalp, according to its laboratory description.[10] It is vascularized by the two facial and superficial temporal pedicles that are harvested separately or in a continuous fashion along the external carotid and jugular axes. It is pierced by three artificial orifices for the nostrils, lips, and eyelids and can be likened to a carnival mask placed over a face, with all its deeper functional structures supposed to be intact and able to adhere to the deep surface of the FAG.[11] It does not, therefore, have any intrinsic motricity, and was not initially described as sensitive.[10,11] It seems, however, technically possible to reinnervate its cutaneous surface by using a deeper dissection plane to

include the three segmental terminal branches of the left and right trigeminal nerves.[12] The name, full face allograft, often suggested to describe this transplant, therefore is somewhat abusive and inexact. Although it covers a wider area than segmental allograft types I, II, or III, this theoretic transplant was devised to resurface extensive burns to the face. Devoid of any functional purpose, it does, however, constitute a partial FAG and, therefore, could be applicable to a hemiface or the whole facial cutaneous cover. In an attempt to avoid any ambiguities with regard to nomenclature, this allograft should be termed partial (type IVp) or a full (type IVf) CTAG of the facial mask.

Strictly speaking, a true full FAG (type V) ought to be performed as a multisegment or composite transplant combining the partial allograft types I, II, and III in a single block of uniform thickness. This would have to be harvested on the entire external carotid axis and the confluent jugular veins on both sides of a donor's head.[13] It would contain all the expression muscles, the common trunks of both facial nerves, and the three segmental branches (V_1, V_2, and V_3) of the two trigeminal nerves. In the deeper planes, it could involve soft tissues only, including superficial musculoaponeurotic system, with or without the periosteal plane[13] (full soft tissue FAG, type VA) or it also could include the maxillary or mandibular arches if necessary (full hard and soft tissue FAG, type VB). Although theoretically conceivable, such allografts correspond to such extensive tissular defects that they hardly ever are encountered clinically. They belong, therefore, more to the realm of virtual or conceptual surgery than practical reality.

To date, clinical experience has focused on allograft types I and II, and in the four documented cases, the composite allografts survived successfully after microsurgical transplantation.[1–5] Three were harvested from a heart-beating donor with a facial morphology comparable to the recipient's,[1,4,5] whereas one was obtained from a cadaveric donor.[3] In none of these cases was partial necrosis of any tissular transplant component reported, and peroperative hemodynamic observation of the allografts showed at all times that the transplant was fully vascularized on unilateral arterial and venous anastomoses (**Fig. 2**). Moreover, wound healing along the lines of cutaneous and mucosal sutures always was fully satisfactory. These results can be explained by the intense anastomotic collateralization of the facial architectural blood vessels (described previously). These results, achieved by four different teams, provide the first evidence of the vascular reliability of face transplants when the fundamental rules of microsurgery are observed.[1–5] Vascular anastomoses always must be performed on large-caliber vessels and should be bilateral, even when the entire transplant can survive on a single vascular axis. Attention to this rule anticipates and prevents the harmful consequences of thrombosis of one of the two arterial or venous axes supplying the transplant. When an allograft predominantly concerns a single hemiface, however, this precaution is not compulsory.[3] Only by extension of these observations to a larger group of patients can these preliminary conclusions be confirmed with regard to the reliability and primary survival of composite FAGs.

BIOLOGIC REJECTION CONTROL AND MEDIUM-TERM VIABILITY OF FACIAL ALLOGRAFTS

Having successfully passed the critical phase of immediate revascularization, the composite FAG must face the challenge of sustainable survival within the recipient's organism. This survival is immediately conditioned by the possibility of controlling biologically the rejection of all its tissular components. Initially, this immunologic challenge was considered the main stumbling block to successful FAT because of the extremely high antigenicity of its main component, skin.[14] The biologic function of skin is a barrier, with many dendritic cells in the dermis and epidermis. Early experiments in primates suggested that a higher level of immunosuppression would be necessary to prevent rejection of CTAGs lined by skin compared with solid monotissular organs in the same animals.[15] Clinical experience gathered from first-hand allografts dispelled these initial fears and showed that once the high-risk period of the first year is over, CTAG rejection could be controlled using similar or lower doses than those commonly used in renal transplantation.[16] Antigenic competition between the various tissues of composite allografts, the induction of blocking antibodies, and activation of regulatory T lymphocytes[17] were the mechanisms evoked to explain these most positive and encouraging observations, which were confirmed by the study of the first three face transplantations.

Hence, classic immunosuppression therapy advocated for the prevention of FAG rejection is no different from successfully tried and tested therapy used in visceral transplantation. Induction immunosuppression comprises infusions of antithymocyte globulin (thymoglobulin coenzyme, for 10 days) along with oral tacrolimus (TRL) a calcineurin inhibitor (target through levels, 10 to 15 ng per mL

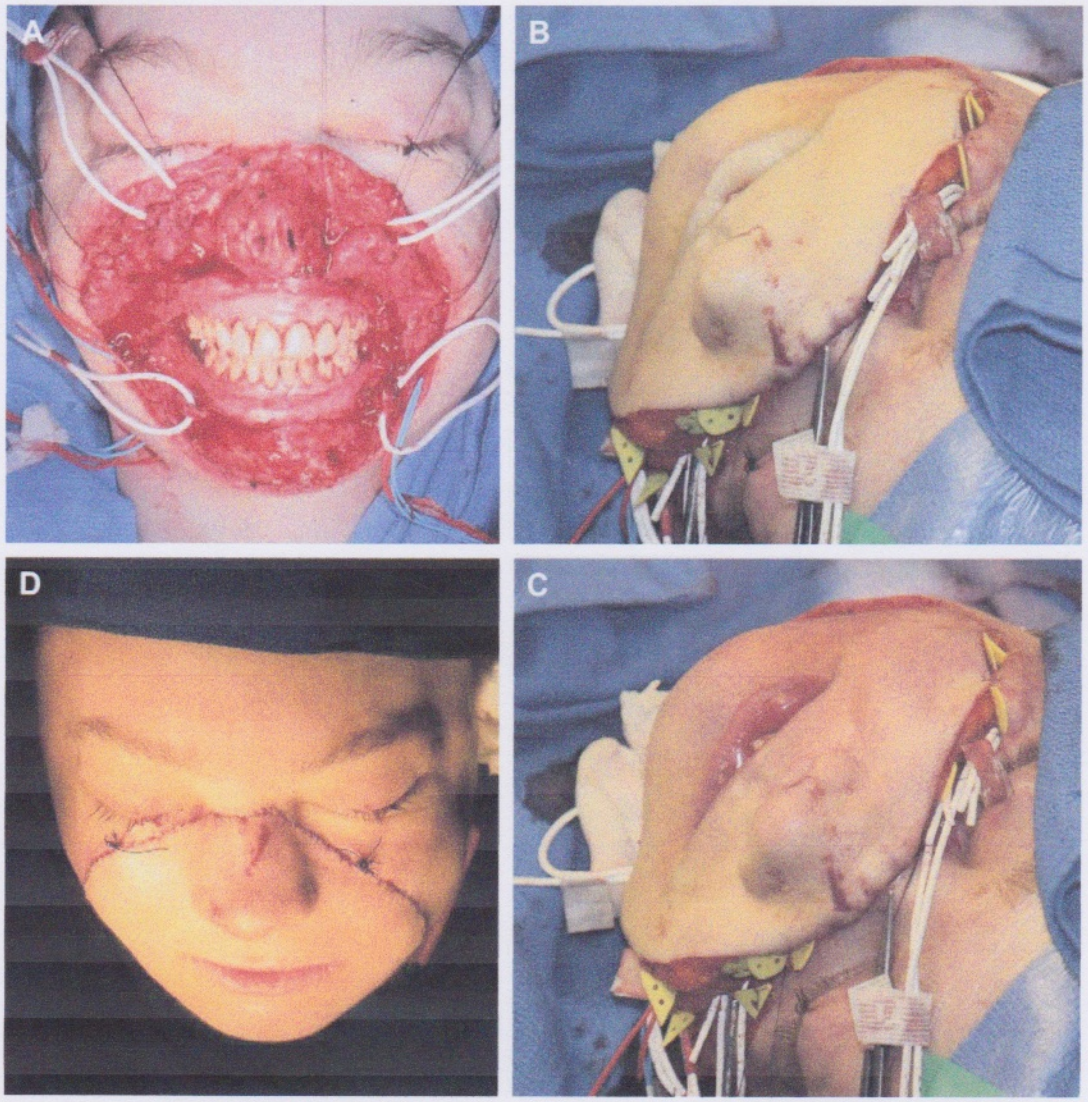

Fig. 2. Immediate survival of a lower central face allograft. Peroperative views showing the fast and complete revascularization of the allograft on a single vascular pedicle. (*A*) Recipient's face anatomic exposure; (*B*) FAG before clamps release; (*C*) FAG 1 minute after clamps release on right facial vessels; and (*D*) 6 hours later, after repair and completion of security bilateral anastomoses. Recipient sensitive nerves are tagged on white laces; recipient blood vessels are exposed on red and blue laces in both submandibular areas. Recipient muscles stumps and facial nerves rami are tagged on stitches. Donor muscles are secured on small silicon rubbers to allow their identification and to prevent their retraction inside the FAG.

throughout the first month), and mycophenolate mofetil (MMF), an antiproliferative agent (2 g per day). These drugs are supplemented with prednisone, administered in rapidly decreasing doses (250 mg on day 1, 100 mg on day 2, then 60 mg/day through day 12, followed by a gradual taper). Additional medication is prescribed for cytomegalovirus and *Pneumocystis jiroveci* prophylaxis.[1,9] Maintenance therapy includes smaller doses of a combination of prednisone, TRL, and MMF (**Fig. 3**).

With the help of these therapeutic regimens, the first three FAGs reported in the medical literature were well tolerated, although all three experienced several rejection episodes with follow-up periods now at 3, 2, and 1.5 years, respectively.[1–5] In the case of the first patient to have benefited from a type I transplant, two rejection episodes were reported,[1,9] at 3 weeks and 8 months postoperatively (see **Fig. 3**). During each of these rejection episodes, cytotoxic activity specifically directed against the donor's antigens could be observed

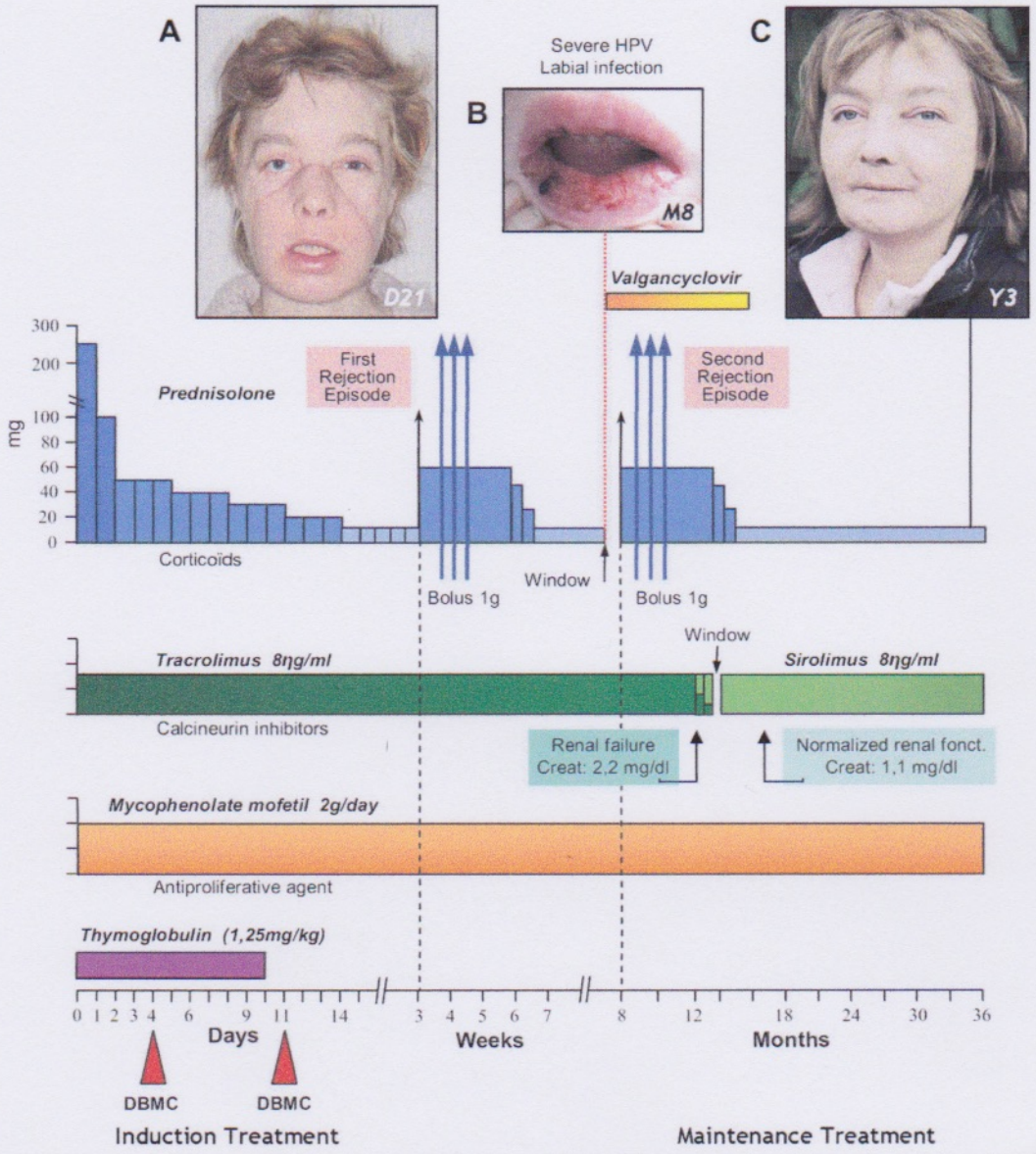

Fig. 3. Immunologic outcomes of the first partial face transplant. Color rectangles indicate the relative doses of immunosupressants used to prevent graft rejection and arrowheads show the two infusions of donor bone marrow cells (DBMC) given during induction treatment. Vertical dotted lines show the two rejection episodes. (*A*) Erythematous aspect of the graft during first rejection. (*B*) Severe human papillomavirus labial infection, just before the second rejection episode. Arrows indicate steroid boluses given to control both episodes. At M 12, a transient renal failure complicated the immunosuppressive treatment but disappeared when TRL was stopped and replaced by sirolimus. Maintenance treatment is characterized by low-doses of immunosuppressant drugs. (*C*) Appearance at 3 years.

in T lymphocytes isolated in the allograft skin.[9] This activity was not observed between the rejection episodes and was found less severe and easier to reverse during the second episode. This first patient's allograft has remained immunologically silent for 33 months. Similarly, the second allograft patient (type IIB) presented with acute signs of allograft rejection at 3, 5, and 17 months post transplantation,[3] and the third patient experienced two episodes, at 1 and 2 months postoperatively.[4]

All rejection episodes without exception were clinically diagnosed as allograft edema and erythema (see **Fig. 3**) and were then objectively

confirmed by biopsies of the transplant mucosa and skin. All the biopsies were grade I or II according to the CTA rejection classification.[18] It also was invariably observed that inflammatory reactions were more intense under the grafted mucosa than under the transplant skin.[9,18] Furthermore, immunohistochemical studies showed that these specific reactions were caused predominantly by CD3+ and CD4+ lymphocytes (T-helper lymphocytes) with few CD8+ cells (cytotoxic lymphocytes).[3,9] In all cases, clinical and histologic rejection signs disappeared completely after a slight increase in TRL and MMF doses, with one or several 1g boluses of prednisone.[3,4,9] Local application of TRL ointment[19] and corticosteroid mouthwashes also were effective.[1,9]

In an unprecedented move, immunologic and therapeutic monitoring of the first FAG was performed using a radial forearm flap harvested from the donor and transplanted to a concealed area of the recipient, namely her left submammary fold.[1,9] This sentinel composite graft, which was revascularized at the same time as the main FAG, has continuously evolved biologically in strict parallelism to the latter. It constitutes, therefore, a valuable and durable skin reserve, particularly useful when iterative biopsies are required for the diagnosis and grading of rejection episodes.[9] Moreover, this sentinel graft allows the objective assessment of the effectiveness of the installed immunosuppression regimen. One further advantage of this indirect monitoring process is that it spares the surface of the main FAG, thereby preventing multiple additional wounds and scarring to the cosmetic appearance of the reconstructed face. It may be argued in opposition to this ancillary procedure, which was in addition to the main graft albeit with no increase in operating time, that it is superfluous because histopathologic monitoring of CTAG could be performed using biopsies of the oral mucosa. Bearing in mind, however, that the monitoring of most FAGs should be fanned out over dozens of years, it is likely that repeated mucosal biopsies would create thick scar tissue under this lining, rendering subsequent biopsies more difficult to interpret and possibly creating invalidating jugal adhesions through contraction.

The favorable results (discussed previously) in relation to medium-term survival of the first few FATs are encouraging and particularly remarkable when compared retrospectively to the initial survival rate of every first visceral allograft.[14] Contrary to the fears initially voiced, they show that rejection of any composite FAG may be routinely controlled with moderate doses of immunosuppressors, thereby proportionally reducing the systemic medical risks associated with them.[17] These observations, however, do not allow in the long term reliably predicting the average lifespan of the allografts, even if this likely survival rate could be extrapolated by analogy with that of other composite grafts from the study of the immunologic behavior of hand allografts over their 10-year history.[17] The risk for chronic rejection, identical to that encountered in visceral transplants, and documented infraclinically in the oral mucosa of one of the face transplant patients, remains real.[3,4] The hope to control these phenomena in the long-term relies on the use of new molecules supposedly more effective and less toxic than those currently used. Some of these promising new drugs are sirolimus, everolimus, active metabolites of FK778 and FK779, and Campath.[14] Some of these drugs have shown, during their phase III studies, that even when administered alone, they are able to reduce the use of immunosuppressors to the sole treatment of rejection episodes and even occasionally to eliminate the need for corticotherapy.[14] Definitive and sustainable biologic control of CTAG rejection will depend on the possibility of manipulating the immune system by inducing a specific state of tolerance against the donor's antigens.[20] Such a state already has been induced at an experimental level in several animal models of CTA.[21–24] In most cases, this entails the creation of a mixed hematopoietic microchimerism or simultaneous allotransplantation of allogenic stem cells, which migrate into the recipient's bloodstream and educate regulatory T cells to specifically recognize the donor's antigens, thereby increasing long-term survival rate of the composite allograft.[25–28] The absence of chronic rejection in most hand transplant patients stems from this phenomenon, as stem cells are supplied by the simultaneous transplantation of allogenic bone marrow within the bones of the distal forearm. The demonstration of CD4+ D25+ FOXp3+ regulatory T cells in the transplanted skin suggests that the donor's hematopoietic stem cells, originating from the vascularized bone graft, migrated there to exert their beneficial effector influence.[29] This observation formed the basis for the addition, at treatment induction on days 4 and 11, of two infusions of hematopoietic stem cells harvested from the donor's bone marrow to the immunosuppression therapy of the first face transplant patient.[1,9]

At follow-up, however, only one of the many analyses of medullary chimerism suggested at month 2 that 0.1% of the bone marrow cells were donor derived.[9] Yet the presence of a microchimerism susceptible of being correlated with the induction of allograft immune tolerance is

classically defined by the threshold value of 1%.[20,25] Although the current results of this clinical trial are not convincing, further research in this area is advocated to develop, on sound objective scientific grounds, tolerance induction protocols that will provide similar results to those observed in several experimental animal models[21–28] or even in certain clinical series reported in solid organ transplantation.[14] There can be no doubt that the future of face transplantation will be conditioned considerably more by progress in the realm of induction of specific sustainable biologic immunotolerance than by surgical factors alone.

FUNCTIONAL RECOVERY OF FACIAL ALLOGRAFTS AND NEUROPHYSIOLOGIC REINTEGRATION WITHIN THE BODY SCHEME

In the author's opinion, a CTA cover to the facial frame is justifiable only if it is a genuine face allograft (ie, a full transfer of all the dynamic players in orofacial function).[1,2] Beyond the undoubted cosmetic benefits of surface and volume restoration in reconstructing extensive defects, it is the possibility of bringing back to life several autonomous functions in the anatomic units transferred that firmly grounds the definitive legitimacy of face transplantation. In addition to its cosmetic aspect, the FAG attains the full status of a genuine organ transplant.[30] It is for this reason that a distinction is made between segmental functional transplants types I, II, or III and the facial mask allograft type IV. In terms of anatomy and neurology, full-thickness allografts are all conceived to enable restoration of all essential sensitive and motor pathways for a balanced relational life characteristic of full facial function.

The observations collated during postoperative follow-up of the first three FAGs reported in the literature[1,3,4] have demonstrated that this ambitious goal could be attained. In all probability, assisted by the neurotrophic effect of TRL, regeneration of sensitive nerves enabled the allografts to recover first their thermalgesic sensitivity, and subsequently their discriminative sensitivity, between the fourth and sixth postoperative months.[9] In relation to motricity, the restoration of facial muscular function is a slower process that can be attained only through intensive physiotherapy initiated as early as the first week after transplantation.[1] When the neuromuscular repairs concern healthy stumps, the restoration of labial contact in a type I allograft may be secured at first partially, then completely between the sixth and eighth postoperative months.[9] From then on, patients recover a normal orbicular function that enables them to feed competently and to emit occlusive phonemes perfectly when speaking. The smile, incomplete at 4 months post transplantation, becomes progressively symmetric between months 10 and 14 and acquires its normal and spontaneous characteristics at approximately 1.5 years (**Fig. 4**). One even more remarkable feature is that the prolongation of dissociated physiotherapy on each of the grafted muscles also enables patients to progressively recruit, for the dissociative mimicry of expressions, the lip elevator muscles to express joy and happiness or those muscles lowering the lips and chin to convey hesitation, sadness, pain, or bitterness.[9] Concomitantly, after the appearance of a wide range of multidirectional expressive movements, the skin of the FAG, initially smooth and motionless, recovers its natural folds that spontaneously generate cutaneous creases and dynamic adipose cushions, particularly in the philtral, mental, and nasogenian areas (see **Fig. 4**). Such motor functional results have never been observed or reported in secondary surgical repair of facial paralysis, not even when resorting to reinnervated autologous muscle transfers.

In correlation with these spectacular sensitive and motor modifications, iterative functional MRI showed, after stagnation of atrophied cortical images of the face for the first 3 postoperative months of the first FAG patient, unquestionable signs of a reorganization of the body image at 4 months (ie, at the exact time of full restoration of the allograft's objective epicritical sensitivity).[9] In parallel with re-expansion of the cortical area corresponding to the face, momentarily invaded by the hand territory during the disfigurement process, reconstruction of the cerebral homunculus is accompanied, in neuropsychologic terms, by an unconscious reappropriation of the allograft in spoken language. At first the patient uses the definite article, "*the* nose, *the* lips" to describe the allograft's anatomic components, but then spontaneously starts to use the possessive form "*my* nose, *my* lips." This phenomenon unquestionably demonstrates that FAG genuinely reintegrates the body scheme at approximately 8 months postoperatively, as it becomes again a dynamic, sensitive, and reactive interface with the outside world. In this fashion, face transplantation perfectly demonstrates, despite its many constraints, its undeniable superiority over conventional autologous reconstruction techniques in disfigurement, the cosmetic results of which are much poorer and the functional consequences always unsatisfactory. Furthermore, it may be added that this type of surgery, although major, produces its multiple results and benefits within a single operation time, with no donor site prejudice.[1]

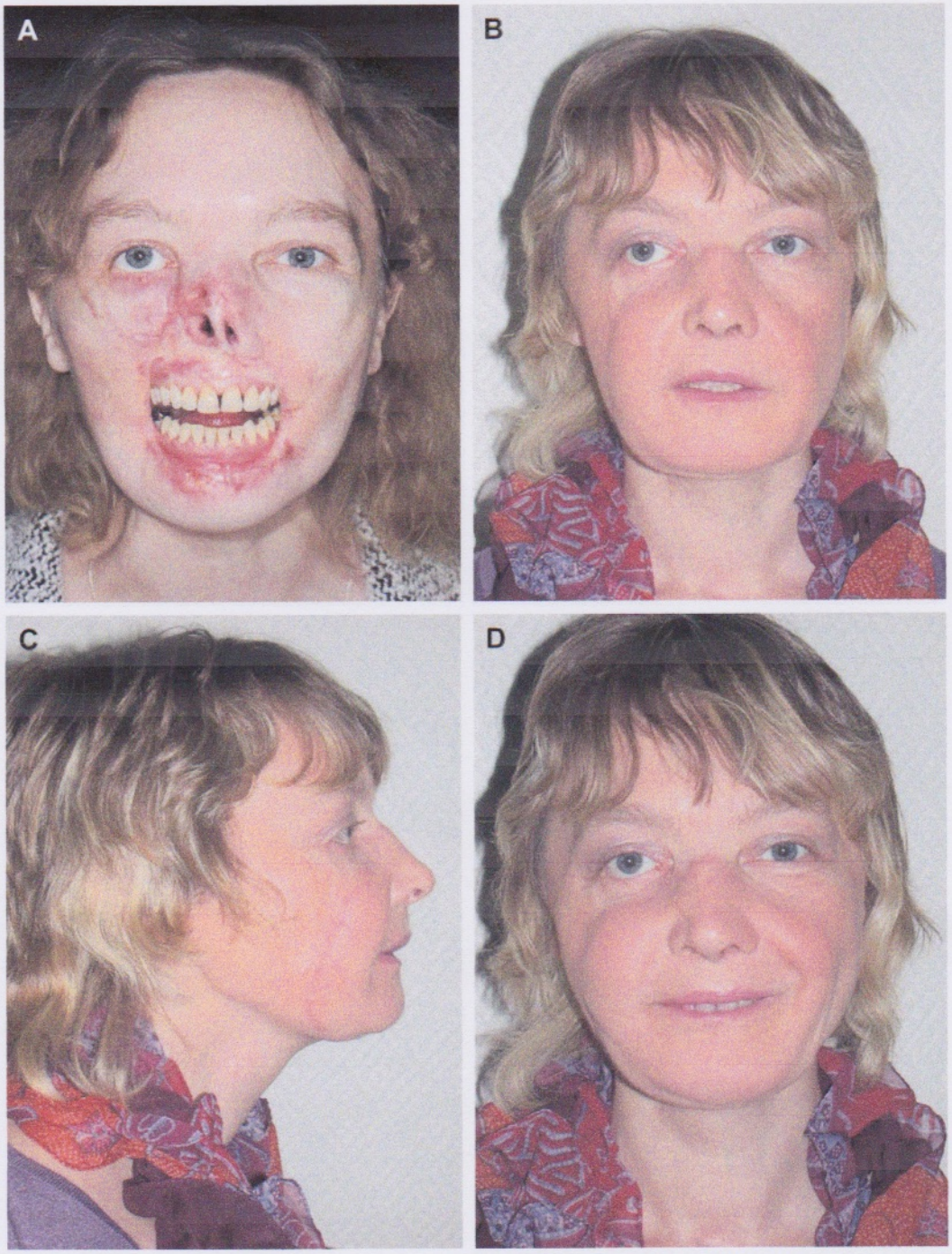

Fig. 4. Cosmetic and functional outcomes of the first lower central face allograft. (*A*) Preoperative aspect; (*B*) 10 months' postoperative frontal view at rest, showing nearly complete passive lip occlusion; (*C*) profile view, emphasizing the quality of contour restoration; and (*D*) smiling appearance, with restoration of multidirectional motions and natural skin plicature.

ETHICAL ISSUES REGARDING THE COST-BENEFIT BALANCE AND RESTORED IDENTITY

Although they seem to justify enthusiasm, the results of the first FATs should not play down that at this stage they are beneficial to only a few patients, follow-up is not yet very long, and many uncertainties remain as to the future of FAT. Face transplantation still is seen as a clinical trial and raises many questions, which not only are medical but also of an extremely profound ethical nature.[30,31] In deontologic practice, every medical gesture, ordinary or innovative, cannot be justified unless the real benefits it offers to patients are considerably more substantial than the potential damaging effects.[32] Yet in the ethical debate that preceded and followed the announcement of the first FATs, many experts estimated their cost-benefit balance as dangerously negative.[2,30–33] The first argument in favor of this negative evaluation is grounded on the potential life-threatening risks to the grafted patients inherent in lifelong immunosuppression imposed to treat a nonvital problem. The second argument addresses the problematics of restored chimeric identity linked to FAG and the potential major psychologic conflict for the recipient.

Concerns about the risks for systemic complications as a result of immunosuppression[32,33] have to be understood in the light of those risks being extrapolated from literature data concerning solid organ transplantation. Many clinicians assumed that the dose of drugs required to control CTAG rejection would probably, because of the high antigenicity of the skin, be significantly higher than that usually prescribed to guarantee the survival of visceral transplants.[34] Now, 80% of renal allografts develop infections and 40% of the postgraft mortality is the result, in this group of patients, to bacterial, viral, or fungal opportunistic infections.[14] Moreover, TRL is nephrotoxic and diabetogenic.[34] The steroids induce other well-known general complications, such as hypertension (15%), osteoporosis (10%), avascular necrosis of the hip (8%), and cataracts (22%).[35] Taken together, immunosuppressants significantly increase the occurrence of skin cancer (14%–20%) and lymphoproliferative disorders (2%–10%) with global incidences varying from 12% to 68% according to the series and immunosuppressant regimen.[14] It seems, however, that these risks extrapolated from retrospective studies of renal transplant patients may not apply to the population of CTA recipients. In a retrospective study, Baumeister and colleagues[36] showed that the number of infectious and organotoxic complications of immunosuppressants was lower in patients who had CTAG in comparison with patients who had renal transplant, as was the incidence of skin cancer (3% at 5 years) and lymphoma (1%). This observation, which can be explained by the fact that the majority of CTA recipients are young and have no associated comorbidity factors, puts these initial fears into perspective.[14,36] It also suggests that face transplant patients may, contrary to the initial assumption, have less general and systemic morbidity linked to immunosuppression than renal transplant patients.

Caution, however, is required in these deductive conclusions. In two of the first face transplant patients, one of two reported rejection episodes was induced after the decrease in immunosuppression because of a local human papillomavirus viral infection in one case and cytomegalovirus sepsis in another.[4] Furthermore, the first face transplant patient is reported to have suffered from transient renal failure as a result of the nephrotoxicity of TRL[9] (see **Fig. 3**). These clinical facts indicate that it remains crucial in the future to be able to dispose of new substitution immunosuppressants, less toxic than the previous generation, to guarantee the continued existence and the further development of face transplantation.[14,32] Finally, in the long term (discussed previously) all hopes of evening out the CTA cost-benefit balance lie in the expected success of experiments aimed at attaining long-lasting immunologic tolerance of the allografts, the survival of which would no longer require any corticosteroid support.[36]

In a correct evaluation of the cost-benefit balance of facial transplantation, the benefits should not be underestimated. The cosmetic and functional grounds have been discussed previously (see **Fig. 4**). They show that, in restoring the essential functions of relational life, such as eating, speaking, and nonverbal expression, FAG essentially is an organ graft.[37] Even if all visceral functions linked to the face are not indispensable to physical survival, all its symbolic functions, profoundly human, are essential for the psychic and social survival of each individual. Reducing the face to a simple image, as some experts do, merely shows a fundamental ignorance of the psychologic problems of dealing with disfiguration and of the profound inner suffering endured by these patients and those around them. By restoring the symbolic and eminently social functions of the face, facial transplantation is an incommensurable life-giving gesture. Thus, it is no different in any other aspect from a kidney transplantation that removes the daily constraints of hemodialysis or from a pancreas transplantation that temporarily curtails the practical constraints of insulin therapy. The only difference between those

three transplantations, which all aim to improve quality of life, lies in that, like a hand transplant, a FAG is immediately visible, whereas the kidney and the pancreas are deeply buried and hidden beneath an abdominal scar.

The immediate and permanent visibility of an FAG is the source of the last ethical issue. This is in relation to the potential ambiguity of the image of self that is restored to a patient thanks to the allograft.[30,31] At the psychologic level, weakened by the disfigurement, that image ambiguity, where, in the mind of the recipient, the allograft remains linked to death, can engender a severe conflict of personality, the harmful consequences of which have been highlighted by the dramatic outcome of the first single hand allograft.[38] Morphologically, however, several virtual imaging[39] and anatomic cadaver[40] studies have shown that the face, when reconstructed by an allograft, although it acquires a mixed image of donor and recipient, retains the main characteristics of the recipient's previous appearance, which is essential for recognition by others. These data have been confirmed clinically by the first receivers of FAGs, who proved capable of recognizing themselves in their new image when looking in a mirror.[1,3,9] At a functional level, the authors have shown, in the prospective neurocognitive assessment of the patient, that her face graft, connected by motor and sensitive nerves to her own brain, had fully recovered, up to the scale of its cortical reorganization at MRI, the role of an autonomous and individual interface with the outside world. Even though the aspect of a recipient's face can never be identically restored by an FAG, a patient recovers not only an anatomic singularity through the operation but also a functional individualization that animates the new face depending on the patient's own feelings. Compared with hand grafts,[16,17,38] the phenomenon of neuropsychologic capture of FAG occurs more rapidly as a transplanted face is not constantly under the eyes of the recipient, so that the "dead," insensitive period, where the allograft does not exist in the relational life, is reduced to the 2 to 3 months necessary for the start of the restoration of sensitivity.[9] With a smile restored, the allograft then definitely belongs to the new individual human history that keeps it alive. In a technical sense, this neurologic fact underlines the cardinal importance of the sensitive and motor nerve anastomoses in ensuring the full success of FAT.[1] The psychologic background of the recipient and close psychiatric support required before and after the transplantation, therefore, are no less important.[31,32] Strict selection of potential recipients, informing them thoroughly, preparing their families, and ensuring their compliance with the rules of follow-up and therapeutic constraints are the last essential conditions to make this undertaking a success.[41] Consequently, every new facial transplantation becomes a unique multidisciplinary challenge that solicits as much intuitive intelligence of the medical team as the different technical skills they embody. All the failures reported in CTA registries have been found attributable to errors of judgment or to the lack of precautions taken regarding the four control parameters (described previously).[17,41]

FUTURE PERSPECTIVES AND CONCLUSIONS

The first facial transplantations, performed only recently, have projected the dreams of science fiction into the real world of science, turning an ancestral myth of humanity related to the image of facial chimera into surgical reality. Spurred by the considerable progress in the field of experimental immunology, these first experiences have shown that, from now on, grafting a face becomes an accessible surgical challenge and that, contrary to previously voiced fears, it is possible to prevent rejection of the composite FAG with the assistance of conventional immunosuppression therapy using small doses of steroids. The functional and neurocognitive results achieved demonstrate the indisputable integration of reinnervated transplants within the body scheme of the recipient patients and the restoration in each of them of a psychologically and socially well-established individual identity.

With these encouraging preliminary data that have partially extinguished the ethical controversy surrounding the principle of FATs, the medical world must move forward, albeit with care. The new field of progress opening engenders many research perspectives that are not only surgical in nature:

- First, in the technical domain, although many anatomic problems already have been solved, the reliability of total facial transplantation remains to be verified by clinical human evidence. Extending the surface of segmental transplants, grouping them in a single multisegmental graft (eg, types I and II), and attaching vascularized bone supports to their deep layer do not present any major obstacles. The main barrier to the application of such extensive grafts in resurfacing severe facial burns stems from the irreversibility of the damage created during preparation of the face for the graft should revascularization or immediate tolerance of the transplant fail.

Traumatic full-thickness facial defects involving several anatomic units of the face, particularly in young and healthy patients, remain, until further investigations, the best indications for the procedure. For reasons of risk-benefit balance, disfigured and already immunosuppressed patients constitute another target population.[42] Some benign tumors and possibly extensive vascular malformations are alternative indications.[4] Less pure than those related to heavy trauma cases, these indications pose the crucial question of whether or not, strategically, their surgical resection should be performed in a dissociated manner from the reconstructive gesture or, alternatively, at the same time as transplantation.

- Subsequently, in the realm of immunology, all future efforts must focus on the development of new combinations of immunosuppressant drugs with fewer, less harmful side effects and on the efficient clinical induction of lasting immune tolerance.[20–23] It is on this last and absolute condition that indications for FAT one day may be extended to the treatment of major substance loss after cancer exeresis.[7] Although these conditions etiologically are unfortunately the most frequently encountered in daily practice, they remain formally excluded from every CTA protocol because of the major risk for tumor recurrence induced by immunosuppression.[14,34]
- Finally, in the field of neuropsychology, the many questions that fed the controversy and the extensive public debate surrounding the legitimacy of FAT have caused the scientific community to ponder the symbolic value of the face and the considerable importance it has in the life of each one of us. Going back to the founding myths of the history of humanity, this reflection brings reconstructive surgeons back to the true dimension of their real mission at the bedside of the sick. Plastic and creative, their noble task consists, first and foremost, of listening, empathy, and compassion. Faced with the intolerable physical and moral suffering of disfigurement, the transgression sometimes represents, at the price of a controlled risk, a duty of humanity (**Fig. 5**).

Half a century ago, while painting his famous *Minotaur and Dead Mare*, in which oddly, the Minotaur, half man, half bull, has a chimeric face, the artist Pablo Picasso evoked the resolutely transgressing character of his art when he wrote, *"I paint against those that have come before me. Not to contradict or betray the works of my great masters, but to raise them up to a new life. You don't have to incessantly repeat what was. You have to create, in the light, what will be tomorrow."* Similarly, CTAs have opened up a new universe of creativity for plastic surgeons in which patients themselves no longer are the only potential donors of tissue transfers necessary for reconstruction. Today's fellow human beings are able to offer a new source of functional made-to-measure transplants that one day may be either more or less extensive than those of today. This creative power that aspires using the achievements of autotransplantation microsurgery to roll back the boundaries of repair surgery with allotransplants is colossal. Consequently, it invests surgeons with new responsibilities of conscience.[43] On that road where progress sometimes oversteps the boundaries of reason and quantification, permanent questioning while acting is a privilege. Similarly, humility remains in the thought that directs the gesture, a duty of elegance[2] that possibly can add to its result a supplement of soul and, thus, humanity.

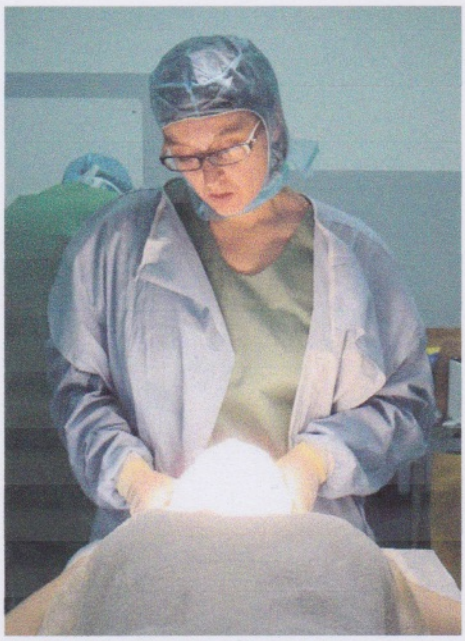

Fig. 5. *Pietà anatomica;* photo by Cédric d'Hauthuille, MD, harvesting team member of the world's first FAT. Ethics and compassion are inherent to any gesture in face transplantation. The restitution of the donor's face image after graft harvesting is a major duty of respect to the donor and the family.

SUMMARY

Once confined to the universe of ancient myth and legend and subsequently the phantasmagoric world of cinema, facial allotransplantation has become a surgical reality. Rendered possible thanks to significant progress of fundamental science, the first successful segmental human face transplants have demonstrated that FAGs are reliable, that their rejection can be prevented by low-dose immunosuppression, and that their neurologic recovery enables all oral and expressive functions of the face to be restored. Moreover, in response to ethical initial objections, the clinical facts have shown that the risk-benefit balance is acceptable in the medium term, that at the neurocognitive level the allograft is reintegrated in the body scheme of the recipient, and that it does not engender a donor identity transfer. In light of these recent advances, this article presents a carefully reasoned classification of FAGs and discusses the resulting different technical, immunologic, and ethical challenges that may lie ahead.

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