

Early reports

Human hand allograft: report on first 6 months

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Summary

Background Long-term survival of animal limb allografts with new immunosuppressant combinations and encouraging results of autologous limb replantations led us to believe that clinical application of hand transplantation in human beings was viable.

Methods On Sept 23, 1998, we transplanted the right distal forearm and hand of a brain-dead man aged 41 years on to a man aged 48 years who had had traumatic amputation of the distal third of his right forearm. The donor's arm was irrigated with UW organ preservation solution at 4°C, amputated 5 cm above the elbow, and transported in a cool container. We dissected the donor limb and the recipient's arm simultaneously to identify anatomical structures. Appropriate lengths of viable structures were matched. Transplantation involved bone fixation, arterial and venous anastomoses (ischaemic time 12.5 h), nerve sutures, joining of muscles and tendons, and skin closure. Immunosuppression included antithymocyte globulins, tacrolimus, mycophenolic acid, and prednisone. Maintenance therapy included tacrolimus, mycophenolic acid, and prednisone. Follow-up included routine post-transplant laboratory tests, skin biopsies, intensive physiotherapy, and psychological support.

Findings The initial postoperative course was uneventful. No surgical complications were seen. Immunosuppression was well tolerated. Mild clinical and histological signs of cutaneous rejection were seen at weeks 8–9 after surgery. These signs disappeared after prednisone dose was increased (from 20 mg/day to 40 mg/day) and topical application of immunosuppressive creams (tacrolimus, clobetasol). Intensive physiotherapy led to satisfactory progress of motor function. Sensory progress (Tinel's sign) was excellent and reached the wrist crease (20 cm) on day 100 for the median and ulnar nerves, and at least 24 cm to the palm by 6 months when deep pressure, but not light touch sensation, could be felt at the mid palm.

Interpretation Hand allotransplantation is technically feasible. Currently available immunosuppression seems to prevent acute rejection. If no further episode of rejection occurs, the functional prognosis of this graft should be similar to if not better than that reported in large series of autoreconstruction.

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Introduction

Hewitt and colleagues¹ predicted that initial clinical trials of hand allografts would occur before the end of the century. This prediction was supported by three main arguments: the good long-term results of autologous replantations in human beings, especially after a clean traumatic amputation,^{2–5} the improvements in experimental limb-allograft results with the introduction of new immunosuppressants, especially tacrolimus^{6–9} and mycophenolic acid,^{10,11} and the data from the few cases of isolated muscle, bone, joint, tendon, nerve, or vascular allografts in human beings.^{12–16} The first human hand transplantation was done at the Edouard Herriot Hospital in Lyon, France, on Sept 23, 1998. The right forearm and hand of a brain-dead male donor aged 41 years was transplanted, on to a male patient who had traumatic mid-forearm amputation. The two team leaders brought together in Lyon an international team of transplant, orthopaedic, and hand surgeons, all skilled in microsurgical techniques, to do the operation. In addition, anaesthesiologists, a specialist psychiatrist and psychoanalyst experienced in body-image disturbances, dermatologists, especially specialists in immunological skin disorders, immunologists, and physiotherapists joined the team. We report the results of this hand allograft for the first 6 months after surgery.

Methods

The patient

The recipient was selected in Sydney from among volunteers who had working forearm muscles and strong motivation, and who were asked to balance an improvement in quality of life against the potential risk of morbidity and mortality of the procedure and long-term immunosuppression.

The chosen recipient was a New Zealand businessman aged 48 years who had moved to Australia and who had had a traumatic circular-saw amputation of his right forearm in 1984. The arm was initially reimplanted but required reamputation in 1989 because of lack of function. The patient refused available aesthetic or functional prostheses and preferred to read relevant studies and make himself available to units contemplating limb transplantation. When he approached the Microsearch Foundation of Australia in Sydney, his expectations were assessed and he underwent a thorough physical examination and psychological assessment. In coordination with Australian

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and French lawyers, and on the advice of the president of the ethics committee of the University of Lyon, we drew up a detailed consent form (available on request from *The Lancet*) and legal contract. This contract included all possible complications related to this potentially life-threatening and non-life-saving procedure, especially known or foreseeable drug-related complications, including short-term and long-term infections, malignant disorders, and other complications that might lead to the amputation of the transplanted limb in the patient's best interest. Surgical and anaesthetic risk, the requirement of special tests, supervised rehabilitation, and long-term psychological support were also detailed. This approach ensured that the patient's consent was given while he was fully aware of the latest available information.

Before hospital admission, the patient was again psychologically assessed by a French psychiatrist and psychoanalyst who was satisfied with the patient's ability to cope with the transplantation. At the first hospital admission, the recipient underwent routine pretransplantation investigations and specific morphological (radiography, arteriography, magnetic resonance imaging) and functional (muscle and nerve charts) tests of the forearm stump.

We identified the following working muscles at stump level: extensor carpi radialis and ulnaris, extensor digitorum communis, pronator teres, brachioradialis, flexor digitorum superficialis, and flexor digitorum profundus. The extensor pollicis longus and flexor pollicis longus muscles were contractile but very small. The patient described phantom-limb sensations of sudden feelings of finger movements, and cramping pain in the hand from time to time, as well as "pins and needles" on exertion of the forearm stump over the past 8 years. Since the recipient was able to play the piano before amputation, he was encouraged to exercise his forearm muscles as if he was playing the piano in preparation for transplantation. We assessed forearm-muscle function by palpation of the muscles during "two handed" finger and hand movements, and checked results against the magnetic resonance images. Some pronation was possible with a functioning pronator teres before surgery.

Donor operation

The donor was a brain-dead man aged 41 years who died from an intracerebral haematoma secondary to skull fracture. The Etablissement Français des Greffes coordinators asked for the family's consent to transplant the limb. A special information form was prepared to help the coordinators to inform the family on the procedure. The donor had the same blood group (O positive) as the recipient and there were six HLA mismatches (A, B, DR); the cross-match was negative. Once brain death was confirmed, the kidneys, heart, and the right forearm were removed. The liver was not removed because of mild steatosis. The hand had slight first-web contracture without thenar atrophy; we did not take this feature to be a contraindication to transplantation. A previous cannulation of the radial artery at the time of admission to the intensive-care unit had not impaired the peripheral blood supply to the limb.

The brachial artery was dissected free 3 cm above the elbow joint and cannulated, and the limb was irrigated with 500 mL of UW organ preservation solution¹⁷ at 4°C, before amputation, a few centimeters above the elbow. The graft was placed in double dry plastic bags and in a standard ice box. The stump was sutured with a rotation skin flap to fit to a custom-made aesthetic prosthesis, which was provided to restore normal appearance.

Recipient operation and graft preparation

Under general anaesthesia, coupled with the administration of a brachial plexus block to achieve optimum postoperative analgesia, vasodilatation, and relaxation, we prepared the recipient's stump by dissecting and identifying all available muscles and neurovascular structures. A tourniquet was applied for haemostasis. The skin incision followed a wide Z line on the palmar aspect and a transverse line dorsally. The anatomical

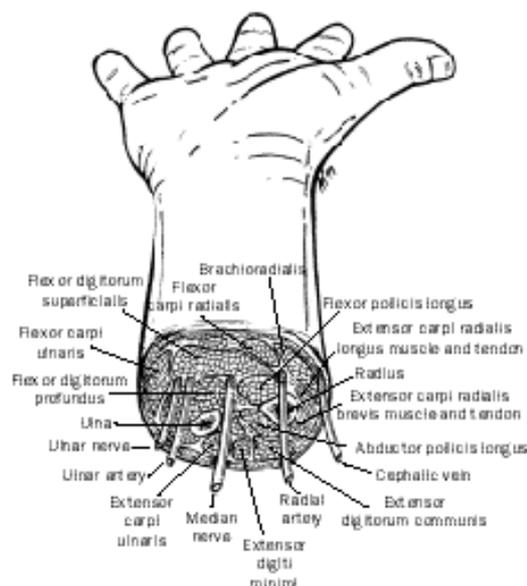


Figure 1: **Anatomical drawing of bony, tendinous, and muscular structures in allograft that were joined and neurovascular structures that were repaired microsurgically in allograft**

structures to be microsurgically joined were sequentially dissected and tagged from palmar to dorsal. These included the median and ulnar nerves and the superficial sensory branch of the radial nerve, the radial, ulnar, and anterior interosseous arteries, the cephalic and basilic veins, and the forearm muscles, which were also tagged individually (figure 1). The recipient's radial and ulnar arteries, as well as the main veins, had been ligated 6–11 cm proximal to the forearm stump and, therefore, much longer donor vascular pedicles were prepared to bridge the gap and to avoid the use of vascular grafts to re-establish blood flow. The forearm bones were transversely cut with an electric saw so that the grafted limb would be the same length as the other.

Concomitant benchwork was done on the procured limb on a bed of iced sponges. Once all structures were ready, the graft was transferred to the main operating table. Osteosynthesis was done with seven-hole plates and 4.5 mm screws. Once bone fixation was accomplished, the tourniquet was released and reapplied. The radial and ulnar arteries were anastomosed end to end with 8/0 prolene sutures. The cephalic vein, which was draining a large network of veins, was anastomosed end to end to a large subcutaneous vein that corresponded to the ulnar vein. The basilic vein was not anastomosed, since no vein of reasonable matching size was identified on the recipient's stump. Total ischaemic time from donor's death to recipient's first arterial clamp removal was 12.5 h. When the tourniquet was released, the hand rapidly achieved a normal colour. The limb was covered with warm wet sponges and left to warm up undisturbed for 20 min. The ulnar and median nerves were microsutured with 9/0 nylon 20 cm and 21 cm, respectively, proximal to the wrist crease. The superficial sensory branch of the radial nerve was not repaired, since the radial nerve on the recipient's stump consisted only of the posterior interosseous branch, and the sensory branch could not be identified.

The muscles were sutured in layers, with attempts to join them individually whenever possible. More particularly, tendons were interwoven to the muscle mass when the degree of repair allowed it. The repaired muscles included the finger flexors and extensors, brachioradialis, and pronator teres. The flexor pollicis longus and extensor pollicis longus muscles were joined to the respective tendons despite the fact that the functioning muscle masses had been assessed before surgery as probably unsatisfactory. A decision was made not to divert other muscles to activate the thumb because of the pre-existing slight first-web-space contracture on the donor hand. We presumed that a

hypothetical possible degree of pre-existing thumb malfunction could preclude the return of thumb flexion and extension. The nerve and muscle repairs were made with the aim of obtaining satisfactory recovery of forearm pronation and supination, wrist flexion and extension, finger flexion and extension, and protective sensation in all fingertips.

Autologous cancellous bone graft chips from the recipient's left iliac crest were harvested and placed around the osteosynthesis sites to assist healing. The skin was sutured directly with the exception of one small dorsal and two small palmar areas, which were grafted with split-thickness skin from the recipient's right thigh. This technique was used to avoid possible postoperative compartment syndrome or excessive tissue tension, and to observe the behaviour of the grafts for viability, since they were sited to cover the recipient and donor muscles. The dorsal skin graft was kept in situ by a tie-over dressing technique. Two subcutaneous penrose-type drains were inserted before the forearm was dressed; the forearm was supported by a plaster volar splint with the elbow flexed at 45° and the wrist extended by 30°. The hand was left uncovered for postoperative monitoring.

Postoperative regimen

The patient weighed 90 kg and was given 1 ampoule (500 units) of heparin subcutaneously on the first day only, and an infusion of 20 mL/h of dextran 40 for the first 6 days, with aspirin 150 mg per day. We administered wide-spectrum antibiotic therapy for 10 days. The induction immunosuppressive protocol consisted initially of antithymocyte globulins (75 mg/day for 10 days), tacrolimus, adjusted to maintain blood concentrations between 10 ng/mL and 15 ng/mL during the first month, mycophenolic acid (2 g/day), and steroids (prednisone 250 mg on day 1 and rapidly tapered to 20 mg/day). CD25 monoclonal antibody was given on day 26 and day 100. Maintenance therapy included tacrolimus (to maintain serum concentrations between 5 ng/mL and 10 ng/mL), mycophenolic acid (2 g/day), and prednisone (20 mg/day at 3 months, 15 mg/day at 6 months).

Physiotherapy was started 10 h after surgery and was offered twice daily for the entire follow-up period. The rehabilitation programme consisted of supervised controlled-motion passive and active exercises, as well as an early sensory re-education and cortical reintegration protocol.

Psychological support was offered once daily during the first 3 weeks, then twice weekly. Skin biopsy samples were taken once weekly from several areas and more frequently if rejection was suspected.

Results

No surgical complications were seen. Wound healing and the take of the skin autografts were satisfactory. There was minor postoperative oedema in the early postoperative period, but it did not prevent the start of the scheduled rehabilitation programme. The blood supply remained always satisfactory, as shown initially by the partial oxygen saturation values in all fingers, and later by scintigraphy.

During the early postoperative period, the patient's general condition was satisfactory. Mild anaemia, secondary to bleeding during surgery because of frequent release of the tourniquet, necessitated blood transfusion and iron supplement therapy. Hyperglycaemia required insulin administration followed by oral hypoglycaemic agents, which coincided with the initial high dose of steroids and tacrolimus. Serum creatinine increased when tacrolimus concentrations were high, but returned to normal with decreases in dose.

In week 8 after surgery, after a decrease in tacrolimus serum concentrations, the skin showed mild disseminated erythema, and biopsy showed a major perivascular dermal infiltrate of mononuclear cells

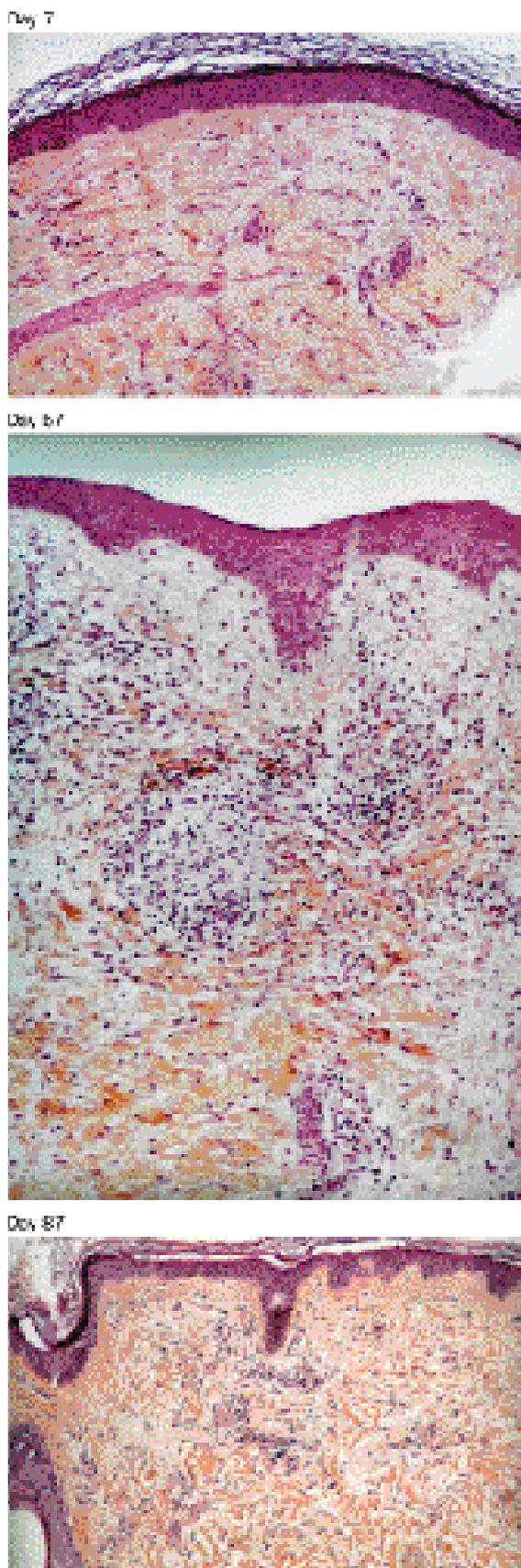


Figure 2: Skin biopsies on days 7, 57, and 85 after transplantation. Day 7, normal epidermis and dermis ($\times 100$, reduced by 55%). Day 57, dense perivascular inflammatory infiltrate of mononuclear cells in upper and mid-dermis, occasional cells in epidermis ($\times 100$). Day 85, epidermis looks normal, dermis contains slight perivascular mononuclear cell infiltrate ($\times 100$, reduced by 55%).

98/2062(3)**4-col****T/C****Figure 3: Patient's hands on day 80**

Dorsal skin autograft seen at upper end of picture. Punch biopsies scars are healed at upper end of allografted skin.

consistent with rejection (figure 2). We increased tacrolimus doses (from 6 mg/day to 14 mg/day) and prednisone doses (from 20 mg/day to 40 mg/day), and topical immunosuppression was started with tacrolimus and clobetasol ointment twice daily. Under this regimen, the redness of the skin faded and was hardly visible after 3 days. Subsequent biopsy samples showed a substantial decrease of the cellular infiltrate.

Passive finger and wrist mobilisation was started on the first day after surgery, fuller finger mobilisation and some wrist mobilisation on day 5, and active mobility at 3 weeks. At 6 weeks, passive mobility of all joints below the elbow was gradually increased, tenodesis effects were encouraged, and active mobility was possible with and without visual control from an early stage. At 100 days, no significant wrist or finger stiffness was seen; slight active flexion and extension of the wrist and long fingers showed that healing had occurred at the musculotendinous junctions. Colour, temperature, and skin texture of the transplanted forearm were satisfactory. The patient did exercises to pinch together the thumb and index fingers, despite the lack of sensation. On day 100, Tinel's sign had advanced to 21 cm on the median nerve and 20 cm on the ulnar nerve and had reached the wrist flexion crease.

At 108 days after transplantation, the patient left Lyon and travelled around the world. He took the standard drugs he had been prescribed, but had no physiotherapy and no supervision by our team. He was seen by a team member at day 165, at which time blood tests were done and a skin biopsy sample was taken, and physiotherapy was restarted. At this stage, skin biopsy showed no rejection and only a slight adjustment was needed in medication. The recipient arrived back in Australia on day 167. Radiography confirmed good callus formation at 3 months and advanced healing at 6 months, with loss of sharp line between donor and recipient bone ends. The radiologist reported also minor porosity of donor hand and radial bones. Nerve regeneration was difficult to assess. Observation of Tinel's sign showed consistent distal progression (from 20 cm at 100 days to at least 24 cm at 165 days). Sensation was assessed in Perth from 175 days to 180 days by repeated Semmes-Weinstein testing (patient blindfolded) and nerve-conduction studies.

At 180 days at centre of palm and palmar surface of proximal metacarpal joints of thumb and index fingers,

the patient had deep-pressure sensation (with microfilament 6–65 g/mm²). Extreme light touch sensation was normal only at 12 cm distal to median and ulnar anastomotic sites (with microfilament 1.65 g/mm²). At 6 months, hair regrowth had occurred on the radial and dorsal borders of hand and forearm. Skin was warm to touch, dry, and pale in colour. The results of repeated careful testing at 6 months contrast the consistent return of the Tinel's sign even to palmar finger surfaces to first interphalangeal skin crease, to the lesser return of sensation confirmed with Semmes-Weinstein and sharp/blunt recognition testing, which puts some return of palmar sensation already beyond the wrist crease but none on the skin area innervated by the superficial sensory branch of the radial nerve, as expected. This rate of return is encouraging.

Discussion

The grafted forearm (figure 3) behaved as an almost ideal reimplantation. In the absence of further rejection, the functional prognosis of motor and sensory recovery should be comparable to those in large series of autoreconstructions.

We have confirmed the technical feasibility of limb transplantation. No technical complications were observed. The skin autografts took completely on the recipient and donor muscles, which is consistent with a good blood supply to the underlying tissues. The clean surgical amputation of the donor upper limb, the relatively short ischaemic time, and preservation with UW organ preservation solution probably contributed to the favourable outcome.

There are many differences between an autoreimplantation and transplantation of a forearm. When an amputated limb is reimplanted, only tissue that remains after avulsion, crushing, or severing trauma is used. Such trauma does severe damage to the various tissues at the site as well as proximally and distally, especially in avulsion and crushing injuries. After such reimplantation, which is mainly a salvage procedure, the patient cannot be expected to regain full function of the traumatised tissue.

By contrast, a donor limb has not been traumatised, and the recipient's remaining length of limb can be dissected back to healthy tissues. In our recipient, the nerves were originally badly traumatised and affected by neuroma formation and degeneration some distance from the surgical amputation site. The radial and ulnar arteries, seen on angiography before surgery, were severely narrowed towards their distal ends. The muscles of the forearm, although exercised for many months and identified preoperatively by palpation and magnetic resonance scan, were not all completely present, or all equally strong. We were able, however, to take the length of donor material that we required, and obtained fresh viable tissue to join together in donor and recipient limbs. Only one venous anastomosis to a big vein draining a large network of veins was done. Venous drainage was satisfactory and no abnormal oedema was seen during follow-up. The usual reimplantation requirement of two veins to adequately drain one artery was not necessary in this case, which presented us with a large number of donor veins issuing into a wide vein suitable for anastomosis to the recipient's large cubital vein. The arteries were anastomosed end to end about

6 cm proximal to the bone joints. The ulnar and median nerves were joined microsurgically by group fascicular technique. There was some regrowth into the palm, to at least 24 cm in 6 months, faster than the rate expected in reimplantation, especially in a patient aged 48 years. Tacrolimus can accelerate functional recovery and nerve regeneration in the rat sciatic-nerve crush model, which may be explained by an increased synthesis of axotomy-induced growth-associated protein (GAP-43).¹⁸⁻²⁰

We could not locate the upper end of the radial nerve in the recipient, but he could weakly contract the hand extensor muscles in the stump before surgery, and has achieved stronger extensor contractions since the operation, which are expected to improve with concentrated physiotherapy.

The single most important obstacle that currently prevents clinical application of limb transplantation is the risks associated with the lack of specific, safe, and effective immunosuppressive therapy. We assumed that the major primary risk was that of rejection, owing to the composite structure of the graft and to the fact that no permanent acceptance of fully mismatched skin allografts has been reported in the absence of tolerance. Therefore, we chose to provide the patient with the most potent immunosuppressive regimen presently available. The skin, a complex immunological structure, is a very immunogenic tissue because of the high numbers of dendritic cells in the epidermis and dermis.^{21,22} On only one occasion did clinical and pathological features suggest skin rejection. The rejection was easily reversed with systemic immunosuppression and administration of topical immunosuppressive creams.²³

One of the main difficulties with composite tissue allotransplantation is the lack of known criteria for acute rejection episodes. We relied on clinical symptoms, serum concentrations of C-reactive protein, and skin biopsy samples. Only the latter proved to be a reliable indicator of dermal rejection, and we cannot exclude the possibility that low-grade or localised rejection episodes may have developed unnoticed in other tissues (foci of hyperfixation observed on bone scan at 3 months may represent minor focal rejection). The bone marrow, a source of allogeneic immunocompetent cells, is a major target for rejection and a source of contamination for donor T cells, which could lead to graft-versus-host disease in a strongly immunosuppressed recipient, and a source of stem cells that might contribute to the development of microchimerism.²⁴⁻²⁶

In addition to efficacy, safety is the main goal of all immunosuppressive treatments in clinical transplantation. In our recipient, side-effects were hyperglycaemia and increased serum creatinine. Hyperglycaemia required several days of insulin administration, and was well controlled by oral antidiabetic drugs, as well as by the concomitant decrease in tacrolimus and steroid doses. On two occasions, serum creatinine increased and returned to normal values when tacrolimus serum concentration decreased. Infections and development of malignant disorders are the most severe complications of immunosuppression. In this recipient, a herpesvirus infection occurred 2 months after transplantation and was easily reversed by acyclovir treatment. No *Pneumocystis carinii* infection was seen in this patient treated with sulphadoxine-pyrimethamine.

The most common malignant disorders induced by

immunosuppression are lymphoid tumours and skin cancers.²⁷ The risk of B-cell lymphoid tumour associated with Epstein-Barr virus is difficult to predict when a combination of new immunosuppressive drugs are given with polyclonal or monoclonal antibodies. The risk probably stays at less than 1%.²⁸ The risk of skin cancer is strikingly higher in Australia—up to 40% of patients develop skin cancers after 10 years of immunosuppressive treatment.²⁹ Decrease in exposure to the sun and increased use of filter creams, as well as early detection and treatment of the lesions, are adequate prevention and therapy of this complication. Although long-term administration of immunosuppressive agents is accepted in visceral organ transplantation, the risks associated with such treatments in patients requiring transplantation of a functional non-vital part of the body should be discussed. This ethical debate is of the utmost importance. We believe that the recipient is the only person able to make an appropriate decision after he or she has received detailed information about the transplant and the immunosuppressive therapy. Our recipient took the initial decision autonomously, while in good mental health and able to balance an improvement in the quality of life against the potential risk of morbidity and mortality.

Risks and benefits were discussed at the USA national consensus workshop on clinical composite tissue allografts in September, 1991.³⁰ In 1993, Nolan and Bowen³¹ investigated 31 scientific papers and concluded that surgeons have the technical capability to do limb allografts. Once drug profiles are improved to have an acceptable risk, functional results are likely to be satisfactory and comparable with those seen after replantation. In 1997, in the closing remarks of the international symposium on composite tissue allotransplantation, the organisers concluded it was time to "just do it".³²

Our recipient's progress has to date strengthened our belief in the protocol we have adopted and we will continue to assess him carefully.

Further studies and trials in human beings are necessary before any final conclusions can be drawn on indications and contraindications of such a procedure. We suggest a multicentre pilot study in cooperation with other interested centres.

Contributors

Jean-Michel Dubernard and Earl Owen organised the procedure. Jean-Michel Dubernard, Xavier Martin, Marwan Dawahra, and Nadey Hakim designed the postoperative immunosuppressive regimen. Earl Owen, Guillaume Herzberg, Mareo Lanzetta, and Hari Kapila designed the surgical protocol and the postoperative physiotherapy plan. All surgical procedures on the donor and the graft were done under the supervision of Jean-Michel Dubernard. The recipient's operation was done under the supervision of Earl Owen. The eight members of the surgical team worked together in the preparation and the transplantation of the graft. All authors contributed to the final version of the paper.

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