DOUBLE HAND TRANSPLANTATION: FUNCTIONAL OUTCOME AFTER 18 MONTHS

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In March 2000, we performed a double hand transplantation on a patient who had suffered traumatic hand amputations 6 years previously. The transplantations were both successful and, 18 months later, the patient has regained some complex hand functions and remarkably good tactile gnosis.

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INTRODUCTION

On March 7, 2000, at the University Hospital of Innsbruck, we transplanted both distal forearms and hands from a brain-dead man to a 47-year-old man with bilateral amputations of the hands at the wrist level (Piza, 2000). The operating team comprised surgeons from the Departments of Plastic and Reconstructive Surgery, Trauma Surgery and Transplantation Surgery, as well as physicians from the Department of Anaesthesiology. Specialists in Physical Medicine and Rehabilitation, physiotherapists and an occupational therapist were responsible for the patient's postoperative care.

Patient selection and evaluation

The recipient patient was a 47-year-old policeman who had lost both hands while trying to defuse a bomb which exploded. The accident also resulted in severely impaired vision in one eye. In 1995 he was fitted with two myoelectric prostheses which enabled him to do desk-work at a police station. Nonetheless, he kept exploring the possibility of hand transplantation to improve his quality of life.

Around this time, reports of hand transplantations in France and the USA (Jones et al., 2000) emerged and a symposium on this issue was organised in Austria in June 1999. Ethicists, legal experts, patient representatives, directors of health insurance companies, surgeons, transplantation specialists, physicians and immunologists participated. In addition, the medical-surgical team at Innsbruck University Hospital which actually carried out the procedure discussed possible improvements in quality of life after transplantation and the potential risks associated with life-long immunosuppression (Doi et al., 1989). They concluded that allograft hand transplantation is justifiable.

The potential hand transplant recipient was admitted to the Innsbruck University Hospital in June 1999 for routine pre-transplantation investigations which included laboratory studies, determination of blood group and human leukocyte antigen (HLA) type, tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV) and radiography, arteriography, magnetic resonance imaging, electromyography, and nerve conduction studies of the forearm stumps. We discussed with the patient the risks associated with surgery and immunosuppressive therapy, including rejection of the graft, the development of a life-threatening infection or malignancy (First and Peddi, 1998), adverse drug effects, and graft amputation. The patient decided to undergo surgery, making this decision of his own free will while in good mental health. Extensive psychological tests were then performed and he underwent mental (imagining movements and the sensation of touch) and physical (strengthening of the muscles of his forearms) training.

OPERATION

Donor operation

The donor was a brain-dead man of similar size, age and build as the potential recipient. The family's consent for the donation of both hands had been obtained. Once brain death was confirmed, we started with the preparation of the right forearm.

All operations were performed by teams acting in synchrony and using tourniquet control. We dissected the donor's and the recipient's arms simultaneously in order to identify all corresponding anatomical structures. The tendons in the donor's arms were dissected as far proximally as possible in order to obtain sufficiently long tendons for transplantation. The anatomical structures to be microsurgically joined were sequentially prepared and tagged, from palmar to dorsal. The tourniquet on the donor's upper arm was removed after careful haemostasis with bipolar coagulation. The brachial artery was then dissected 3 cm above the elbow joint and cannulated: after tendon dissection, the limb was irrigated with 500 ml of University of Wisconsin (UW) organ preservation solution at 4°.

With the forearm in neutral rotation, an osteotomy was performed in the middle third, so that sufficient length of the forearm bones was available for the

placement of 7-hole low contact dynamic compression plates (LCDCP). The arm was then transferred to the adjoining operating theatre. The same procedure was performed some hours later on the left arm.

The donor stumps were sutured to fit custom-made aesthetic hand prostheses.

Recipient operation

Simultaneous to the donor operation, the recipient was prepared in the adjoining operating theatre. Under general anaesthesia and with tourniquet control, we first prepared the recipient's right stump and dissected and identified all available muscles and neuro-vascular structures. The periosteum of the forearm bones was elevated together with the interosseous membrane, leaving a proximally based periosteal flap. The level of osteotomy was chosen to allow stable placement of a 7-hole LCDCP plate. After osteotomy, the donor and recipient bones were aligned in neutral forearm rotation and stabilized with these plates. The periosteal flap was then placed over the osteotomy. 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, and the basilic vein were anastomosed. Tendons were interwoven with the muscles. The ulnar, median and superficial sensory branch of the radial nerve were repaired using microsurgical techniques with 9/0 nylon, 10 to 12 cm proximal to the wrist crease. The skin was similarly closed except for a 6 cm × 6 cm palmar area which was grafted with split-thickness skin from the recipient.

The same procedure was performed on the left arm. The muscles of the left forearm were not as well preserved as those on the right, and some were nonexistent. There were no flexor digitorum superficialis (FDS) muscles and only the flexor digitorum profundus (FDP) muscles for the ring and little fingers. Recipient-to-donor repair of the extensor pollicis brevis (EPB) and abductor pollicis longus (APL) was performed en masse. Recipient-to-donor repair of the tendons of the FDP to the index finger and the flexor pollicis longus (FPL) was performed. We had to transpose the extensor carpi radialis longus (ECRL) to the FDP (index and middle fingers) and the extensor digitorum communis (EDC) of the index and middle fingers to all of the fingers' EDC. The extensor pollicis longus (EPL), the extensor indicis proprius (EIP) and extensor digiti minimi were missing. We used a 10 cm-long homologous artery graft from the donor for reconstruction of the ulnar artery.

The total ischaemia time was 150 minutes for the right hand and 170 minutes for the left. The hands were left uncovered for postoperative monitoring, but the arms were placed in long-arm splints.

Postoperative care

The patient was transferred to the Intensive Transplantation Care Unit, where he was given immunosuppressive and physical therapy.

Immunosuppressive therapy and infection prophylaxis

Induction therapy with anti-thymocyte globulin (2.5 mg/kg) was begun during surgery and continued until day 4. Before revascularization of the first graft, the patient received 500 mg of methylprednisolone intravenously, followed by 250 mg on day 1 and 125 mg on day 2. Thereafter, oral prednisolone was prescribed, which was rapidly reduced to 25 mg on day 8 and then gradually tapered to 15 mg by day 15 and 10 mg by day 200. Since the end of the first year, the patient has been on a maintenance dose of 7.5 mg oral prednisolone. Tacrolimus was administered orally twice daily: the initial dosage of 0.20 mg/kg was adjusted to maintain trough levels (as measured with the IM_x Tacrolimus II assay: Abbott, Vienna, Austria) of 15 mg/ml during the first postoperative month, 12 mg/ml during months 2–6 and 10 mg/ml thereafter. In addition, the patient was given 2 × 1 g of micophenolate mofetil (Jones et al., 1999).

Since the donor was positive and the recipient negative for CMV, prophylaxis with ganciclovir was started on day 1 at 2 × 200 mg intravenously per day for 6 days and then changed to 3 × 1 g orally, Cotrimoxazole for prophylaxis against *Pneumocystis carinii* infection was administered orally (960 mg daily).

Rehabilitation programme

Intensive physical therapy led to satisfactory restoration of the patient's sensory and motor functions. Rehabilitation was started on the 3rd postoperative day, and was based on our protocol for replantation (a modified version of that of MacNeil and Gordon, 1996).This therapy included an early protective joint motion programme (EPM I and II). From the beginning, the patient was given special Perfetti (Perfetti, 1986; Perfetti, 1997) cognitive exercise training, which includes sensory re-education and cortical reintegration (Foltys, 2000; Hunter et al., 1995; Lurija, 1998). Sensory nerve regeneration, as determined by Tinel's sign, was excellent and reached the MP joints by 6 months. Electrical stimulation was started in the 4th postoperative week, occupational therapy 1 week later and EMG-biofeedback training was initiated 9 months after surgery. This rehabilitation programme was performed 5 hours/day, five times/week, for a period of 12 months. The patient was provided with thermoplastic splints for correct finger and wrist placement, as well as for temporary muscle function substitution. He was trained to be independent in all basic activities of daily life. Some aids, such as specially designed grips for cutlery and keys, were provided. The patient was trained to write

with a pen and use a computer keyboard. Improvements in strength, movement and sensibility progress were regularly monitored and documented. Repeated Semmes-Weinstein tests with the patient blindfolded and nerve-conduction studies were performed.

RESULTS

Skin, wound and bone healing occurred without complication. Nerve regeneration, as assessed by the presence of Tinel's sign, progressed more rapidly than had been anticipated based on our experience with replantation (Doolabh and Mackinnon, 1999; Fansa et al., 1999; Gold, 1999). Tinel's sign was noted in the palm (15 cm from the coaptation of the nerves) after 3 months and in the fingertips after 6 months. One area of skin graft necrosis occurred in week 2 and was treated by débridement and an autologous skin graft. When CMV replication was first diagnosed on day 41, the patient was switched first to Foscavir and then on day 128 to Cidofocir (435 mg/14 days). Eight months after transplantation, the patient was again negative for CMV.

In week 8 diffuse disseminated erythema appeared on the skin of both hands. A skin biopsy revealed moderately acute cellular rejection, characterized by moderate perivascular and dermal lymphocytic infiltration and mild epidermal degeneration. This was treated with 750 mg methylprednisolone and 500 mg prednisolone for 2 days, as well as the topical application of tacrolimus ointment for 3 weeks (Yuzawa et al., 1996). The lesions resolved completely within 2 weeks, and a further biopsy then showed normal skin. The rash also disappeared completely within a few days. In the 9th postoperative month, an arteriovenous fistula in the left forearm was detected by ultrasonography and was clipped. Since then, no further surgical intervention has been necessary.

The patient was discharged from the hospital on day 59 after surgery. He then underwent rehabilitation as an outpatient for 9 months. Eighteen months after surgery, the patient is in excellent general health with normal renal function (creatinine 0.9 mg/100 ml), normal liver function and normal blood pressure (140/80 mm Hg). He is negative for CMV and EBV.

Functional recovery

From the first day, the patient regarded the new hands as his own. After 1 year, temperature, pain, pressure sensation and two point discrimination (right hand from 5 to 8 mm, left from 6 to 12 mm) sensation were present in both hand and fingers, and hair growth had occurred. The skin was warm to the touch, and some regeneration of the sweat glands had occurred. There was EMG evidence of abductor digiti minimi innervation in both hands, and slight adduction and abduction of the fingers was possible. The patient had a grip strength of 14.0 kg in his right hand and 8.5 kg in his left, a key pinch strength of 1.3 kg for the right thumb and 1.1 kg for the left with a lateral pinch strength of 0.4 kg on the right side. The active ranges of motion of the forearm and wrist and flexion of the fingers 1 year after transplantation are shown in Tables 1 and 2. The patient can now use both hands to perform many functional activities (Figs. 1–4) which he had not been able to perform before with his prostheses. These include turning the pages of a newspaper, writing with a pen or pencil, using a computer, dialling and using the phone, eating with a knife and fork, holding and drinking from a glass, taking care of his personal hygiene, and dressing himself. However, he still finds it difficult to perform activities which demand fine motor coordination, such as buttoning a shirt. The patient went back to work 9 months after surgery. After 18 months he rode a motorcycle more than 300 km, to visit us in Innsbruck. Although his vision is still impaired in the eye injured in the accident, he has adequate vision in the other, allowing him to resume his passion for motorcycling.

DISCUSSION

Hands are needed for almost every activity of our daily lives. They are also an essential part of our appearance, are vital to our development, and play an important role in determining our personality (Herndon, 2000).

Hand transplantation is an opportunity to restore a patient's sense of touch as well as his physical appearance and function (Francois et al., 2000; Lundborg, 1999). No prosthesis can offer the sensations of touch, pressure and pain that are necessary for normal hand function. At present not even the best prosthesis is an adequate substitute for a hand (Graham et al., 1998), even a hand with reduced sensitivity and motor

Table 1—Active wrist and forearm movements at 14 months

	Extension/flexion	*Ulnar/radial deviation*	*Forearm rotation*
Right	50-0-20	20-0-10	85-0-90
Left	35-0-10	5-0-15	60-0-75

Table 2—Active palm-pulp distances (cm) after hand transplantation

	3 months	*6 months*	*12 months*
Right hand			
Index	4.5	1	0
Middle	3	1	1
Ring	2.5	0.5	0
Little	2	0.5	0
Left hand			
Index	5	3	2
Middle	6	3.5	3
Ring	5.5	3	3
Little	4.5	2.5	2.5

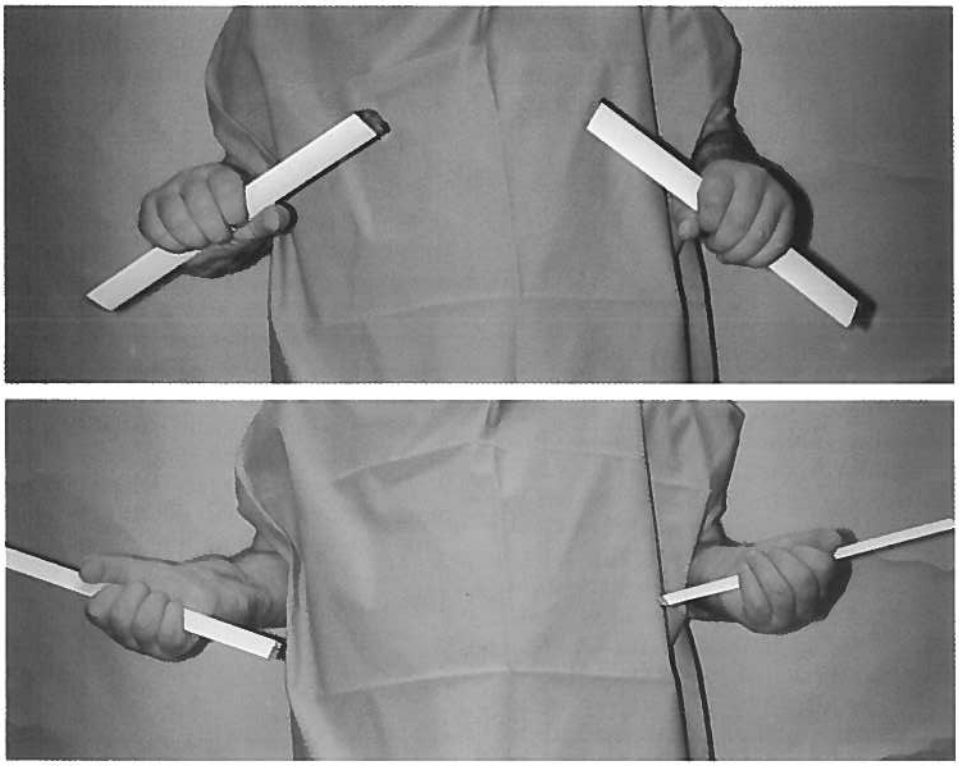

Fig 1 Pronation and supination of forearms.

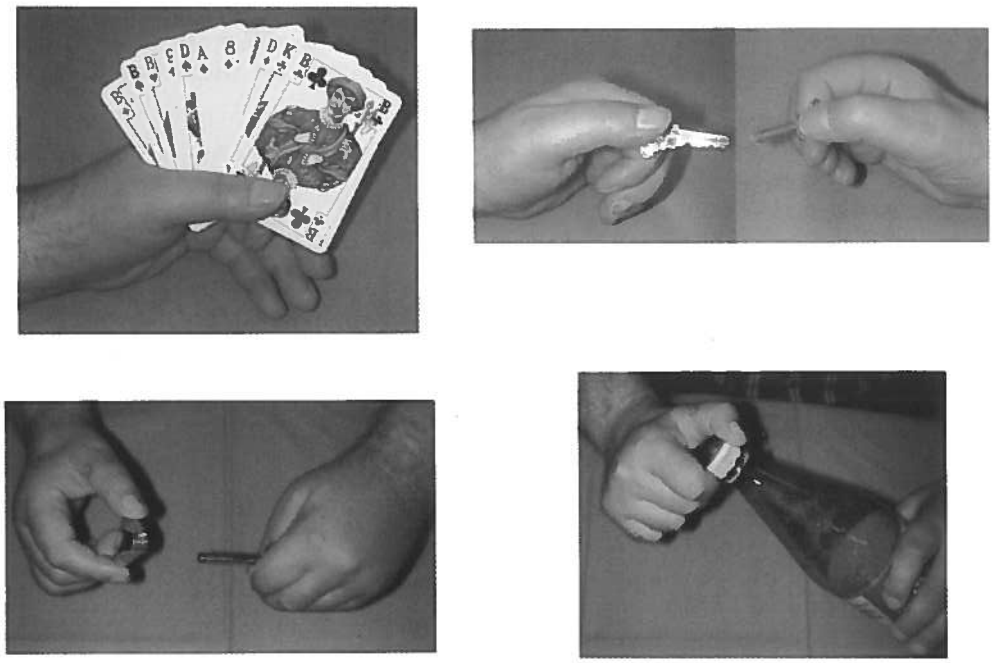

Fig 2 Hand functions.

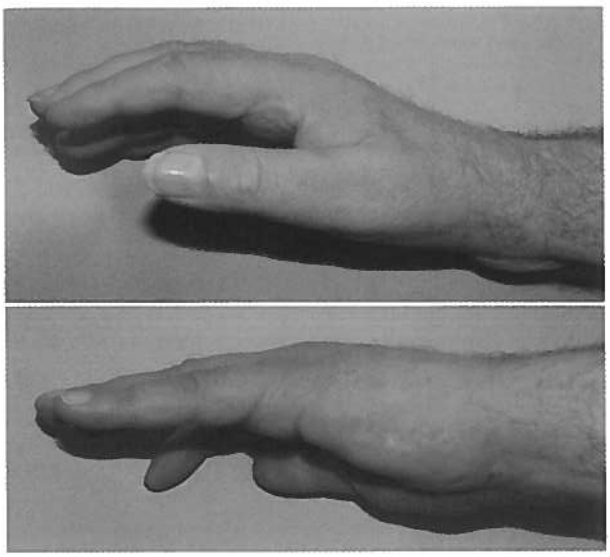

Fig 3 (a) Right and (b) left hands with fingers in extension. The index finger of the left hand can be extended only when the patient makes a specific, concentrated effort to do so.

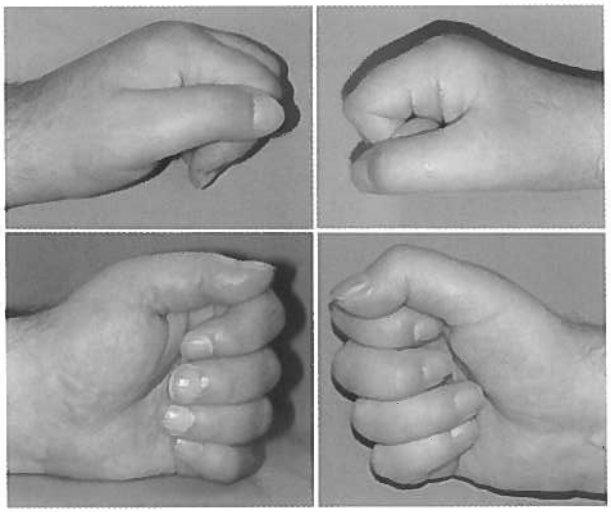

Fig 4 (a) Left and (b) right hands with flexion of the thumbs and fingers.

function. If the level of amputation and transplantation can be planned in advance, the ischaemia time minimized and atraumatic surgery performed, good results can be expected.

The surgical technique is relatively straightforward: microsurgery and the other technical problems associated with a double hand transplantation do not differ greatly from those encountered with replantation (Dubernard et al., 1999; Jones et al., 2000; Meyer, 1985; Russell et al., 1984). However, a patient will have to undergo life-long immunosuppressive therapy (Meiser et al., 1999) and the associated risks represent the greatest dilemma with limb transplantation. This must be balanced with the expected improved quality of life of the patient.

The ideal recipient should fulfil several criteria. First, he should have lost both hands (Jones et al., 2000) as the coordination between the brain and intact hand is so good and automatic in single hand amputees that it is extremely difficult to train the transplanted hand: In fact, this can only be done by actively suppressing the intact hand. A second indication for transplantation is an eye injury or impaired vision. Blind people, or those with impaired vision, have an enhanced sense of touch and extremely sensitive hands, as demonstrated by the reading of Braille.

The forearm stump should ideally end in the distal third, and it is better if both stumps are the same, or nearly the same length. The recipient should demonstrate ability to cope with stress and strain, an unwavering desire to have functioning and feeling hands, and a willingness to comply totally with the medical regimen. He must be strong enough to deal with the constant sight of hands that remind him of the donor cadaver and be able to accept the new hands as his own. He must also have adequate family and psychosocial support, be intelligent enough to fully understand the information given to him and be able and willing to communicate with his therapy team. Ideally, the team of doctors should belong to one hospital and speak the same language as the patient, since communication is of vital importance.

In the final analysis, the success of an allograft transplantation is not defined by revascularization and survival of the transplant, but by the acquisition of complex hand functions and the integration of the transplanted hand into the daily life of the recipient, as well as into his self image. Whether it is justified to treat a non-life-threatening condition with a life-threatening procedure cannot be answered with a simple yes or no. Progress in immunotherapy research in the future should reduce the risks of the procedure.

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