

# Composite Tissue Allotransplantation (CTA): Current Status and Future Insights

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## Abstract

Approximately 7 million individuals (over 1 million amputees) require complex reconstructive procedures in the United States each year. The recent success of clinical composite tissue allotransplantation, attests to the fact that composite tissue allografts have tremendous potential in these life-enhancing reconstructions.

This review summarizes the initial outcomes of the first four human hand transplants, together with those of the first larynx, bone, knee, nerve and tendon transplants, with special emphasis on the operative technique, graft survival and functional outcomes. The May 2000 Louisville symposium, where these results were presented was undoubtedly a milestone in the history of modern composite tissue allotransplantation. It set the stage for reconstructive and transplant surgeons, researchers, physiotherapists, patients and patient advocates and members of the community to convene and discuss major advances in current composite tissue allotransplantation. The symposium underscored the vital importance of objective evaluation of the status of composite tissue allotransplantation by frank dissemination of details of clinical results and complications of the transplants performed thus far.

The composite tissue allotransplantation area is among the newest of transplant areas. The immunology of composite tissue allografts is complex, making tolerance more difficult to achieve than organ tolerance. It needs to be emphasized that any episodes of acute rejection should be prevented for perfect restoration of function and to minimize the risk of chronic rejection in composite tissue allografts. Efficacious,

safe and ethical clinical tolerance protocols could improve patient acceptance of composite tissue allografts by providing an alternative to chronic immunosuppression.

## Key Words

Composite tissue · Hand · Larynx · Bone · Tendon · Nerve · Allotransplantation · Rehabilitation · Immunosuppression · Tolerance

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## Introduction

This article summarizes the proceedings of the 2nd International Symposium on Composite Tissue Allotransplantation (CTA) held on May 17-18, 2000 in Louisville, Kentucky, USA. This historic meeting brought together teams from around the world that performed the first clinical composite tissue allotransplants in the form of hand, larynx, bone, knee, nerve, and tendon. In addition to these teams, experts in several related fields (reconstructive and transplant surgery, immunology, research, medical ethics, rehabilitation, organ procurement, transplant psychiatry) as well as the recipients of a larynx and a hand transplant came together to learn from these first clinical cases and to discuss the road ahead.

To put the work presented at the May 2001 meeting into context first, we will provide a brief history of some key events that have brought CTA to where it is today. The concept of CTA for restoration of congenital or

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acquired deformities is not new. In fact, one of the first accounts of transplantation dates back to c. 348 A.D. in which the sainted twins Cosmas and Damien replaced the gangrenous, cancerous leg of a sleeping man with that of a recently deceased Ethiopian Moor [1]. This important contribution to medicine was immortalized a century later in the famous painting of "The Legend of the Black Leg" by Jacopo da Varagine in 1270 A.D. [2]. Then in the 16th century in Bologna, Italy, Gaspare Tagliacozzi, who many regard as the "father of plastic surgery", reportedly used a flap of tissue transplanted from a slave to reconstruct the severed nose of a man. The story goes that the reconstructed nose survived for 3 years, until its donor died, at which time it rejected [3, 4].

It was not until the turn of the 20th century, that groundbreaking advances in vascular surgery served as harbingers for the modern era of CTA. Carrel in 1908 described the first successful orthotopic canine hind limb transplant [5]. At the same time, Judet and Lexer reported animal and clinical whole joint allotransplants [6, 7]. In 1912, Guthrie reported the first canine heterotopic head transplants [8]. While these early studies were instrumental in advancing surgical transplantation techniques, further progress was blocked by immunologic rejection. Then in the early 1950s, the pioneering work of Gibson, Medawar, Billingham and Brent in Britain and Owen in the USA began to probe the causes of rejection and laid the foundation for the field of transplantation immunology as we know it today [9–12].

The early 1950s saw Murray et al [13] and Hamburger et al [14] perform the first successful kidney transplants, leading to a rapid expansion of the field of solid organ transplantation. This success in solid organ transplantation led a team of surgeons in Ecuador to perform the first cadaveric hand transplant in 1964. Unfortunately, the immunosuppressive regimen used [azathioprine (AZA) and hydrocortisone] was insufficient and the hand rejected and subsequently amputated 2 weeks post transplant [15, 16].

In the late 1970s and early 1980s, three separate groups performed upper extremity transplants in primates with the then revolutionary new drug cyclosporine [17–20]. While rejection was suppressed for periods of up to 296 days in these studies, the skin component of the transplanted upper extremities was in most cases rejected within the first months following transplantation. In addition, the high doses of cyclosporine A (CsA), required to prevent the limbs from rejecting in these primate studies, were too toxic to

be used in humans. The discouraging results in Ecuador, together with those reported in these primate studies, forced reconstructive surgeons to abandon further attempts to transplant hands for the next two decades.

In 1989 and 1991, Kniha et al [21], Randzio et al [22], and Gold et al [23] described successful allotransplantation of hemi-mandibles in rabbits, as well as in monkeys, using cyclosporine to prevent rejection. From these and other studies, it became apparent that cyclosporine/AZA/steroid-based regimens were capable of preventing rejection of select types of composite tissue allografts that did not contain a skin component. These findings led to the use of cyclosporine/AZA/steroid-based regimens in a series of clinical CTAs to reconstruct nerve, tendon, muscle, and bone, joint and laryngeal deficits. Transplantation of composite tissue allografts that involved a skin component, however, was considered impossible with these regimens.

At this same time, in September 1991, a conference on the clinical use of CTA was held in conjunction with the Rehabilitation Research and Development Service of the U.S. Department of Veterans Affairs in Washington, DC [24]. The purpose of the conference was to determine "the clinical feasibility of transplanting limbs in patients with limb loss" and "the direction in which clinically oriented limb transplantation research should head". The conference participants concluded that CTA would be clinically possible in the near future and that "historic" initial trials [25] would occur within the next 2–5 years.

6 years later, no limb transplants had been performed, and another CTA meeting (1st International Symposium on CTA) was held in November 1997, in Louisville, Kentucky, USA. At this meeting, reconstructive and transplant surgeons, immunologists, scientists, and ethicists from around the world came together to discuss "the scientific, clinical, and ethical barriers standing in the way of performing the first successful human hand transplant" [26]. After 2 days of heated debate, a general consensus was reached that the first hand transplant "could be done today" using current drug regimens. This was best expressed in the closing remarks of the conference proceedings that the time had come to "just do it" [27].

Around the time of this meeting, our institution in Louisville was in the midst of performing a series of experiments in a preclinical swine forelimb model that demonstrated tacrolimus/MMF (mycophenolate mofetil)/prednisone therapy successfully prevented

composite tissue allograft rejection, while causing minimal systemic toxicity [28–31]. Based on these findings [32], in 1998 and 1999 teams in Lyon, France [33, 34], Louisville, Kentucky, USA [35], and Guangzhou, China, performed the first four successful human hand transplants using tacrolimus/MMF/prednisone-based combination therapy. Besides, at the time this review was submitted for publication, eleven additional cadaveric hand transplants were reported in seven patients from around the world. This includes our second patient.

The initial outcomes of the first four human hand transplants, together with those of the first larynx, bone, knee, nerve and tendon transplants were presented by the teams that performed them, at the May 17–18, 2000 CTA symposium in Louisville, Kentucky, USA. In this concise review of the proceedings of this landmark symposium, we summarize these findings with special emphasis on the operative technique, graft survival, and functional outcomes. For a detailed description of the proceedings of this meeting, the reader is directed to a special edition of the journal *Microsurgery* (December 2000) [36].

### Current Status of CTA

#### Human Laryngeal Transplantation

Strome et al [37] of the Cleveland Clinic performed the first successful human total laryngeal transplantation on January 4, 1998. Kluyskens & Ringoir [38] made an unsuccessful attempt at subtotal laryngeal transplantation earlier in 1969.

*Clinical History.* The larynx recipient was a 41-year-old male patient. His laryngotracheal complex was completely destroyed 20 years ago in a freak motorcycle accident involving a steel wire strung across a road. Despite multiple surgical attempts, it was impossible to reconstruct, and he had to use an electrolarynx for 19 years. He was otherwise healthy on preoperative assessment except for a history of hypertension.

*Operative Procedure.* In a 12-h operation, the donor larynx was transplanted whole along with a composite of 70% of the pharynx, five tracheal rings, the total thyroid and parathyroids. The transplant had bilateral microvascular arterial and venous anastomoses. Further, sensory and motor neuronal units were reestablished. Further details of management are beyond the scope of this review.

*Immunosuppression Regime.* The induction protocol was a combination of cyclosporine (10 mg/kg), AZA (5 mg/kg), solumedrol (1 g initially, then 50 mg/6 h), and

OKT3. After the 1st month, the AZA was replaced with MMF (2 g/day), and the cyclosporine dose reduced. 1 year after the surgery, cyclosporine was substituted with tacrolimus. At present, the patient is on tacrolimus (10–15 ng/ml), MMF (2 g/day), and prednisone (8 mg/day).

*Graft Survival and Functional Outcome.* By the time of the Louisville meeting, it was almost 2½ years after the transplantation had been performed. The functional outcome of the transplant was excellent. Sensory return was achieved at 3–4 months and motor function detected at 6 months after transplantation. Cosmesis was good, aspiration was minimal, and the transplanted thyroid/parathyroid complex was functional. The recipient had serviceable speech and normal swallowing. He had good pitch control despite a patent laryngostomy. The degree of functional return was corroborated when the larynx recipient “spoke” at the meeting. It was a remarkable experience for the audience to hear a man speak with a “transplanted voice” about his views on the risks versus the benefits of the transplant he had received [39].

*Complications.* No significant complications related to the operative procedure itself were noted. The patient experienced a decrease in vocal quality at 13 months post transplant due to mucosal edema secondary to a rejection episode associated with tapering of the cyclosporine dose.

#### Human Femur and Knee Joint Transplantation

The results of three femoral diaphyseal allotransplants and five knee joint allotransplants [40] performed by Hofmann et al of Germany since 1994 were presented at the meeting [41].

*Clinical History.* All the three recipients of femur allotransplants were males in the age range 21–54 years. Chronic recurrent osteomyelitis was the indication in the first two patients and chondrosarcoma (grade I) in the third patient. All patients were unsuccessfully managed by surgery and had bone defects that were unsuitable for lengthening techniques. The bone defects secondary to osteomyelitis were 12 cm and 14 cm, and 33 cm in the patient with chondrosarcoma.

Four of the five recipients of the knee joint allotransplants were males in the age range 17–47 years. The fifth patient was a female aged 34 years. Traumatic destruction of the knee joint with total loss of extensor mechanism was the indication in all patients. The bone defects involved both the distal femoral (10–15 cm) and proximal tibial (5–10 cm) aspects of the knee joints.

Whole joint allotransplantation was the only alternative to arthrodesis or amputation.

*Operative Procedure.* Thorough asepsis was achieved in the bony defects using extensive surgical debridement followed by jet irrigation of nonviable tissue and antimicrobial wound dressings. Soft tissue coverage was attempted where possible using local or free flaps. The femur and tibia were stabilized using a hinge arthroplasty device after compression nailing. Passive mobility was maintained using physiotherapy, and CsA was started to determine tolerance to the drug. Vascular and collateral patency was confirmed with angiograms.

The femoral and knee joint allotransplants were performed using a lateral approach to the thigh and an anterior approach, respectively. The donor bone grafts (with their quadriceps tendons) were precision cut under radiographic control to match the defects, and osteosyntheses were performed with intramedullary interlocking compression nails. The vessels were anastomosed and quadriceps apparatus repaired.

*Immunosuppression Regime.* All patients received CsA (1.5 mg/kg i.v.), AZA (1.5 mg/kg i.v.), antithymocyte globulin (4 mg/kg i.v.), and methylprednisolone (250 mg) for the first 3 days. In the first 6 months, a combination of CsA (6.0 mg/kg p.o.), and AZA (3.0 mg/kg p.o.) was used. Thereafter, all patients received CsA alone. Immunosuppression was withdrawn in the femur transplant patients when bone union at the osteotomy was confirmed on X-ray.

*Graft Survival and Functional Outcome.* Despite complications, all the femur transplants eventually regained full weight bearing. Four of the five knee joint recipients were mobile at the time of discharge (3–8 weeks postoperatively) and regained full weight bearing 2–4 weeks later. Movement ranged from full extension to 120° flexion. Two of them have done well without major complications at 29 and 45 months postoperatively.

*Complications.* The clinical course of the eight patients was full of complications related to the immunosuppression. Most importantly, cytomegalovirus (CMV) infection, deep vein thrombosis, and recurrent deep infection were the treatable complications noted in the femur allotransplant patients. In one patient, an additional total knee arthroplasty was necessary distal to the femoral transplant due to posttraumatic gonarthrosis. In one knee joint recipient, a fatigue fracture of the tibial plateau was detected. One femur transplant and one knee joint allograft had to be

removed at 18 months and at 1 week post transplant, respectively, due to recurrent infection. Other complications were improper control of allograft rejection by the drugs used and inability to easily monitor rejection in the deep-seated bone allograft.

#### Human Nerve Transplantation

The results of a total of seven peripheral nerve allografts performed by Mackinnon et al [42] at Washington University since 1992 were presented at the meeting.

*Clinical History.* The patients ranged in age from 3–24 years. The indication for nerve transplantation was massive peripheral nerve deficit secondary to trauma that could not be reconstructed conventionally. Four upper extremity and three lower extremity nerve transplantations were performed. Of these, two patients exclusively received nerve allografts and five patients received a combination of auto- and allografts [43, 44].

*Operative Procedure.* The total allograft length varied from 72 cm in a 3-year-old patient, to 350 cm in a 16-year-old patient. All allografts were harvested fresh and used immediately. In case subsequent reconstructions were necessary, grafts were stored in University of Wisconsin solution.

*Immunosuppression Regime.* The first three cases were treated with cyclosporine, AZA, and prednisone, while the subsequent four cases received tacrolimus instead of cyclosporine in a similar protocol. In all cases, immunosuppression was withdrawn upon detection of a positive Tinel's in the distal segment of the nerve.

*Graft Survival and Functional Outcome.* Recovery of sensory and/or motor function was detected in six out of seven patients. While all of them had sensory recovery, three cases also experienced motor recovery. No deterioration of nerve function was observed after withdrawal of immunosuppression.

*Complications.* One patient rejected the allograft. No other immunosuppression- or surgery-related complications were noted.

#### Human Tendon and Muscle Transplantation

The only two reported cases of vascularized tendon allotransplantation are credited to Guimberteau et al [45]. The tendon was derived from a living donor in one case and a cadaveric donor in the other. Both cases were treated with cyclosporine (6 mg/kg/day) for 6 months. Functional recovery in both cases was good with no complications.

A single case of muscle allotransplantation was reported at the 1st International Symposium on CTA at Louisville, Kentucky, USA, in 1997. The recipient was a 56-year-old male renal transplant patient, who also had a frontoparietal scalp defect after cancer resection. The defect was repaired using a rectus abdominis muscle allograft from a cadaveric donor. Immunosuppression consisted of cyclosporine and prednisone [46].

#### Human Hand Transplantation

A hand transplant, by virtue of its unique composition of tissues that include skin, muscle, tendon, nerve, vessel, lymph nodes, bone and bone marrow, can be considered to be the "gold standard" in CTA. In this regard, no other organ or tissue transplant matches the hand transplant in its immunogenicity as well as complexity. Four hand transplant procedures performed by three teams were reported at the Louisville meeting [47]. By this time, all the four transplant recipients were beyond their 6-month follow-up after the surgery and functional return could be assessed. The cases presented were a right hand transplanted in Lyon, France, on September 23, 1998 [33]; a left hand transplanted in Louisville, Kentucky, USA, on January 23, 1999 [35]; and two right hands transplanted to two recipients in Guangzhou, China.

**Clinical History.** The ages of the hand transplant recipients were 48 (Lyon), 37 (Louisville), and 39 and 27 (Guangzhou). The ages of the hand donors were 41 (Lyon), 58 (Louisville), and 29 and 24 (Guangzhou). All the recipients and donors of the hand transplants were males. The Lyon recipient lost his hand to a circular saw, the Louisville recipient lost his after a firecracker explosion, and the two Guangzhou recipients lost their hands in an explosion and a steel wire accident, respectively. The Lyon recipient was transplanted 14 years after he had lost his hand and the Louisville recipient 13 years after his limb loss. Both of the Guangzhou recipients were transplanted only 2 years after they had lost their hands. Prior medical history was unremarkable in all recipients except for a history of diabetes in the Louisville recipient.

**Operative Procedure.** Details of operative technique are beyond the scope of this review. Key factors given consideration during surgical planning were: anatomic level of donor limb harvest, preparation of donor limb, ischemia time, perioperative medications (other than immunosuppressive drugs). All surgeries

were performed under broad antibiotic coverage and anticoagulation therapy.

The Lyon team harvested the donor limb 5 cm above the elbow, whereas the Louisville and Guangzhou teams harvested the donor limbs at the level of the elbow (dislocation).

Ischemia times ranged from approximately 6 h for each of the two Guangzhou recipients, 5 h for the Lyon recipient, and 12 h for the Louisville recipient.

All donor hands were perfused with University of Wisconsin solution immediately after harvest and were stored in cold (4 °C) solution until they were transplanted. The Guangzhou team scraped and washed out the radial and ulnar bone marrow in both donor limbs and in addition, irradiated one of the donor hands with 8 Gy (1 Gy = 100 rad = 1 J/kg) prior to transplantation.

Because of the more distal level of amputation in the Louisville and the two Guangzhou recipients, tendon-tendon repairs were possible between the donor limbs and the recipients. Since the level of amputation in the Lyon recipient was close to the elbow, tendons of the donor forearm muscles were sutured to the forearm muscle bellies of the recipient. The levels of nerve coaptation were different in the different cases.

**Immunosuppression Regime.** The induction protocol for the Lyon and Guangzhou recipients was with antithymocyte globulin, whereas the Louisville recipient received basiliximab. Thereafter, a similar tacrolimus-based combination regimen with tacrolimus (5–10 ng/ml), MMF (ranging between 0.75 and 3 g/day), and prednisone (ranging between 10 and 25 mg/day) was used in all patients.

**Graft Survival and Functional Outcome.** At the time of publication of this review (2001), the transplanted hand of the Lyon recipient was amputated due to non-compliance with his medication. All other transplanted hands continue to do well without complication, the first Louisville patient being the longest surviving hand transplant in the world (29 months).

The tests performed to assess hand function were range of motion (ROM), grip and pinch strength, Tinel's sign, Semmes-Weinstein and Carroll's test. The ROM for the transplanted hands of the Louisville and both Guangzhou recipients, although not back to normal, were similar and sufficient for good function. No results were obtained from the Lyon recipient. Tinel's sign was positive at the fingertips at 4 months post transplant in the Guangzhou recipients and at 6 months in the Louisville and Lyon recipients. The Guangzhou

recipients had the best results for grip and pinch strength, followed by the Louisville recipient and finally the Lyon recipient.

The Semmes-Weinstein test is performed with monofilaments and measures pressure sensitivity: at 6 months follow-up, the Lyon recipient had deep-pressure sensation on the palmar surface of his transplanted hand (unfortunately we could not obtain later results). At 16 months follow-up, the Louisville recipient had sensation ranging from diminished protection to loss of protection on the palmar surfaces of his transplanted hand. This test was not used in the Guangzhou recipients.

In the Louisville and Guangzhou recipients, mobility, motor function, and sensation were integrated using the Carroll test. This test assesses and compares functional recovery as it relates to activities of daily living (ADL). It consists of different tasks ranging from placing cubes on a shelf, to manipulating different-size metal balls between the thumb and other fingers and placing them in a basket. The results of this test in these recipients can be described as fair to good by the scheme developed by Russel et al [48], and are comparable to the results obtained after forearm replantation [49].

**Complications.** No intra- or perioperative complications were noted in the four transplants (when presented at the meeting).

## Discussion

### Current Status of CTA

The successes of the limited number of clinical cases performed so far attest to the fact that technical challenges related to operative procedure or management can be overcome. However, further advancement of CTA into the clinical arena continues to be curtailed by concerns of prolonged immunosuppression that recipients must be subjected to [50]. The primary controversy is that these procedures are performed for quality-of-life issues, not life-saving issues [51, 52].

**Tolerance Induction in CTA.** A major focus of current transplantation research is the development of strategies to obviate the need for immunosuppressive drugs by inducing specific tolerance to transplanted tissues. Unprecedented progress in understanding of the immune response has successfully resulted in tolerance induction in small animal models. Nevertheless, it has been difficult to reproduce such success in humans or even in primate models. The three most important developments in research for tolerance induction in CTA were discussed at the meeting.

The use of “co-stimulatory blockade” to prevent allograft rejection was presented by Elster et al [53]. Fundamentally, activated recipient T-cells cause rejection. Such activation requires at least two signals. Interference of one of these signals using certain antibodies results in death of recipient T-cells attacking the donor tissue, thus preventing rejection.

The use of anti-CD3 and deoxyspergualin was presented by Thomas et al [54]. CD3 is a molecule that is present on the majority of T-cells and is crucial for their function. Blockade of this molecule with specific “anti-CD3” antibodies will prevent the rejection response.

The use of mixed allogeneic chimerism in tolerance induction in CTA [55] was presented by Christina Kaufmann. When donor bone marrow containing stem cells is transplanted in a treated recipient, the newly developing recipient T-cells begin to see donor cells as “self”. Therefore, the recipient perceives an organ from the same marrow donor as “self” and accepts it without immunosuppression. Current clinical trials using this method are under way in kidney transplantation.

**Rehabilitation in CTA.** Unlike solid organ transplants, where physiologic function of the allograft is predominantly dependent on systemic and immunologic factors, return of function (both sensory and motor) after CTA like hand transplants is, in addition, crucially dependent upon active rehabilitation. The excellent results of the rehabilitation program for the Louisville hand transplant patient presented at the meeting [56] underscored the role of active physiotherapy in restoration of function after CTA, however good the surgical technique might be.

### Future Insights

Continued success in clinical CTA over the next few years could convince the transplant community to shed its skepticism, that all attempts at CTA are ambitious and misguided. The CTA area is among the newest of transplant areas [57]. The immunology of CTA grafts is complex, making CTA tolerance more difficult to achieve than organ tolerance. It needs to be emphasized that any episodes of acute rejection should be prevented for perfect restoration of function as well as to minimize the risk of chronic rejection in CTA. Efficacious, safe and ethical clinical tolerance protocols could improve patient acceptance of CTA by providing an alternative to chronic immunosuppression. The May 2000 Louisville symposium was undoubtedly a milestone in the history of modern CTA. It set the stage for

physicians, scientists, patients, and members of the community to get together and discuss the major current contributions to the advancement of CTA. Critical issues in CTA like organ procurement and establishing a transplant registry were also discussed [58]. Most importantly, this meeting highlighted the unique collaboration of two distinct specialties: plastic/hand surgery and transplant surgery. Reports on the first successful composite tissue allografts presented at the meeting stand testimony to this cooperative endeavor. Future meetings will hopefully host exciting new developments in CTA, help in sharing of research ideas and findings, and make CTA a widespread treatment modality to the needy patient population.

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