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The History of Human Composite Tissue Allotransplantation

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ABSTRACT

Restoration of amputations and disfigurement are represented in ancient mythology, but the modern history of composite tissue allotransplantation begins with World War II injuries that generated seminal immunologic experiments by Medawar and co-workers. These studies led to the first successful human allografts in the 1950s by Peacock with composite tissue and Murray and co-workers with solid organs. Pharmacologic immunosuppression brought rapid growth of solid organ transplantation over the next 50 years, but composite tissue transplantation virtually disappeared. This evolution was judged to be a consequence of the greater antigenicity of skin, which that was insurmountable by the available immunosuppression. In the mid-1990s, progress in immunosupression allowed skin-bearing grafts, led by successful hand transplants, which produced a renaissance in composite tissue allotransplantation. Since then, graft types have expanded to over 10, and graft numbers to over 150, with success rates that equal or exceed solid organs. The field has emerged as one of the most exciting in contemporary medicine, although accompanied by substantial challenges and controversy. This paper reviews the origins and progress of this field, assessing its potential for future evolution.

THE DESIRE TO REPLACE lost limbs and facial features is as old as human trauma, and deeply imprinted in our psyche. It is represented in myths, such as the story of third-century twin physicians, saints Cosmos and Damian, who reappeared after martyrdom to transfer a leg from a Moor to an esteemed churchman.[1–3] In reality, ancient transplantation attempts all failed, and success existed only in myth and misrepresentations until 50 years ago.

The modern field of transplantation biology began during World War II, with the goals of allografting skin and composite tissue for reconstruction of severe burn deformities suffered by Allied sailors from U-boat attacks and pilots from the Battle of Britain. To pursue these goals, biologist Peter Medawar joined plastic surgeon Thomas Gibson and co-workers in pioneering experiments of skin allograft immunology at the Plastic Surgery Unit in Glasgow, Scotland, where these war victims were treated.[4] Medawar's subsequent landmark work led to Knighthood and a 1960 Nobel Prize.

ORIGINS OF CLINICAL TRANSPLANTATION

Repeated failure in experimental skin allotransplantation turned the efforts of early investigators to other possibilities. Renal allotransplantation emerged as the most promising.[5] A landmark step toward that goal occurred in 1954, when Joseph E. Murray, John P. Merrill, and J. Hartwell Harrison in Boston performed the first successful human organ isograft, a kidney donated between identical twins.[6,7] The first successful human allograft followed 3 years later. It was also the first composite tissue allograft (CTA)—an en bloc digital flexor tendon mechanism CTA by visionary North Carolina plastic surgeon, Erle E. Peacock, Jr., in 1957.[8,9] In 1959, Murray, Merrill, and Harrison accomplished the first successful organ allograft, with renal grafts between fraternal twins using total body irradiation.[10,11] Success was rare until the era of pharmacologic immunosuppression, which was launched by seminal studies with the purine analog, 6-mercaptopurine, by Charles Zukoski and Roy Calne in 1960.[12,13] Widespread clinical application came with development of a precursor, azathioprine (Imuran),

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by George Hitchings and Gertrude Elion, and its clinical introduction by Murray and Calne in 1962.[14–16] During the last third of the 20th century, liver, heart, lung, pancreas, and small bowel allotransplantation were all realized as drug regimens improved.[14–17] For his pioneering work, Murray became the only plastic surgeon to receive the Nobel Prize in Medicine.[5]

THE ORIGINS OF COMPOSITE TISSUE TRANSPLANTATION: FLEXOR TENDON MECHANISMS

History has virtually forgotten the first successful human allografts. Nevertheless, Peacock's landmark 1957 case was the origin of clinical CTA and stands with the 1954 renal isograft by Murray, Merrill, and Harrison, their 1959 renal allograft, and the advent of pharmacologic immunosuppression in the 1960s as the founding events of human transplantation.

Peacock devised his procedure to address the unsolved problem of end-stage flexor tendon incarceration after failed salvage attempts with autografts.[8,9,18] His flexor tendon mechanism grafts from cadavers were done without immunosuppression, and were vascularized by inosculation. His elegant preclinical animal studies showed minimal allograft antigenicity and no detectable structural degradation over time.[19] The significant element transplanted was the gliding space created by the synovial membrane lining the sublimis and profundus tendons, the collagenous pulleys and sheath, the vascular vinculae, and the attached cartilaginous volar plates. To differentiate these structurally complex grafts of multiple tissue lines from the solid organ grafts then being contemplated, Peacock originated the term "composite tissue allografts."

Ultimately, over 40 of these flexor tendon mechanism CTAs were done by a handful of clinician–investigators, with over a 70% salvage rate for end-stage flexor tendon incarceration, which previously had no solution beyond amputation.[18] The technique was later replaced by introduction of the silicone rod, which allowed reconstruction by pulley autografts and silicone rod–generated pseudosheaths followed by staged tendon autografts. This salvage method produced comparable outcomes to CTAs without the complicated logistics of donor graft procurement.

More than 25 years elapsed between Peacock's flexor tendon mechanism CTAs and the next clinical CTA successes, which were also flexor tendon mechanisms by an alternative technique reported by J.C. Guimberteau in 1992.[20,21] He twice transplanted these CTAs, using vascular pedicles from the ulnar artery and temporary immunosuppression. In his small series, however, no advantage was shown over Peacock's original CTA technique, or its successor, the silicone rod pseudosheath and tendon autograft.

EARLY HAND TRANSPLANTATION ATTEMPTS

Renal allograft success led to the first attempted hand CTA by surgeon Robert Gilbert of Ecuador, reported in 1964.[22] He transplanted 1 hand to a bilateral amputee with technical success, using azathioprine and prednisone immunosuppression. However, irreversible acute rejection followed, necessitating graft amputation at 3 weeks.[23] This outcome, plus total failures in experimental animals, led all to conclude that skin and skin-bearing structures were too antigenic for transplantation.[24,25] Clinical efforts were abandoned, and more than 30 years passed before any successful skin-bearing CTAs.

Shortly after Gilbert's failed hand CTA, Peacock and associate John W. Madden in North Carolina nearly succeeded with a hand transplant between identical twins. One sister was on life support with an irreversible brain injury, and the other had a burn equivalent of amputation at the wrist level. Skin grafts were successfully exchanged, but the recipient called off the transplant at the last moment because of psychologic stress from contemplation of "wearing" her sister's hand. (Personal communications with Erle E. Peacock, Jr., MD, and John W. Madden, MD). In retrospect, this was the first sign of the powerful role of identity and related psychologic issues in CTA, which would reappear prominently in hand and face CTA considerations 35 years later.

THE MODERN ERA: A CTA RENAISSANCE

In the 25 years after Peacock's first human CTAs, there were no reported clinical successes in hand or other composite structures. Virtually all investigators believed that epithelium had such great antigenicity that it was insurmountable by immunosuppressive drugs.[24,25] During this long hiatus, calcineurin inhibitors appeared, with cyclosporine use established in the 1980s and tacrolimus in the early 1990s.[17,26] These greatly increased solid organ graft success, and showed benefit in animal CTA experiments, but did not lead to human trials.[27] By the mid-1900s, however, a new purine analog, mycophenolic acid, emerged.[28] This, along with calcineurin inhibitors, produced repeatable long-term survival in skin-bearing rat limb grafts.[29] Noting this, we formed a team to study hand and face transplantation at the University of Louisville in Kentucky. We confirmed the rat limb studies and reproduced them in a large animal preclinical model.[30,31] This led to the organization of clinical hand CTA teams in Louisville and Lyon, France. The first hand CTAs were by the teams assembled in Lyon under Jean-Michel Dubernard in September 1998, and by our team in Louisville led by Warren Breidenbach in January 1999.[32–34] In January 2000, the first bilateral hand CTA was done by Dubernard and co-workers in Lyon.[35]

At the same time experimental hand CTA studies began in Louisville, Gunther Hofmann and co-workers were pioneering clinical knee and femur CTAs in Germany.[36–38] Also, Marshal Strome and co-workers at the Cleveland Clinic were studying experimental laryngeal CTAs, which led to their groundbreaking clinical CTA in 1998.[39]

Those initial CTAs led to organization of more than a dozen CTA programs internationally, and graft types were expanded beyond hand, larynx, and knee/femur, to include

face, abdominal wall, peripheral nerve, tongue, scalp, uterus, and penis. Over 100 clinical CTAs have been done since the mid 1990s, in addition to the 40 or 50 earlier flexor tendon mechanisms.

UPPER EXTREMITY TRANSPLANTATION

After the initial hand CTAs in Lyon and Louisville, teams organized in 6 additional European sites and 5 sites in China performed over 45 hand CTAs in more than 35 recipients.[40] These grafts were about equally divided between unilateral and bilateral recipients. All were for wrist to mid-forearm amputations, except for 2 partial hand grafts in China, and a 2008 bilateral above-elbow graft in Germany. All were technically successful with no early vascular failures. Immunosuppression has been with the same drugs and doses as renal transplants, and no grafts were lost to early, acute rejection. In patients compliant with medication and rehabilitation, excellent function resulted, with return of sensory, motor, and overall function essentially equivalent to replants at the same level. Complications mirror the renal transplant experience for recipients on the same medications and doses. The initial Louisville patient has the longest surviving CTA, at 10 years in January 2009.

The first 2 hand CTAs provided paradigms defining subsequent world experience. The Louisville patient was carefully selected with thorough psychological screening, preparation, and family involvement.[41–44] He was disciplined in rehabilitation, in taking medication, and in ongoing monitoring. His resultant outcome compares with the best of hand replantations in objective measurements and restored activities of daily living, and he and his family are highly satisfied. This pattern has been repeated in subsequent United States and European recipients, where thorough psychological screening and preparation is standard, where immunosuppression is provided, and where close, ongoing monitoring is routine.[40,45]

The single exception to the Western experience was the first recipient of the team in Lyon.[32,33] He was a unilateral amputee from New Zealand transplanted in September 1998. The procedure went well, but the recipient prematurely left the care of his physicians against advice. He abandoned rehabilitation, and took immunosuppressive drugs in an irregular and unmonitored fashion. As a result, he never acquired more than minimal motor function or range of motion, and progressive rejection and withering over several months resulted. Two years after transplantation, he requested amputation from members of the original team.[33,46] This outcome reinforced early controversy surrounding these CTAs.[44,47–49]

This pattern of progressive rejection and atrophy from insufficient immunosuppression occurred in all hand CTAs in China.[50] Although all were initially successful, the health care system of China changed, and recipients were left responsible for purchasing their own immunosuppressive drugs, which were unaffordable. Immunosuppression withdrawal led to no successful outcomes.

Thus, all hand allograft losses to date have come from either poor psychological screening or loss of access to immunosuppression, and success correlates with thorough psychosocial screening, preoperative education, intense rehabilitation therapy, assurance of ongoing medications, and close follow-up.

TRANSPLANTATION OF FACIAL STRUCTURES

At the beginning of the Louisville CTA project, we recognized craniomaxillofacial CTAs to be technically possible and would meet valid clinical needs. However, facial CTAs presented much more complex problems with exit strategies and with peer, public, and organ procurement organization acceptance. We judged that hands should become the first CTAs. Five years of hand CTA observations and ethical discussions on face CTAs followed.[51–56] The first facial CTA was done by Devauchelle, Dubernard, and co-workers in November 2005, in Amiens, France.[57] The recipient suffered loss of all lip tissues, nose, and central cheeks from a severe dog bite. Lip sensation and motor function returned over the first 6 months, with subsequent gradual improvement to produce high-quality functional and esthetic results.[58] A second facial CTA was done in April 2006 by Guo and co-workers in Xian, China, for a recipient who lost the right side of his face in a bear attack.[59] Progressive functional return over the first 6 months produced a good esthetic result with a minor revision at 6 months.[60] The third facial CTA was done by Lantieri and co-workers in Paris in January 2007 for exceptionally deforming, advanced neurofibromatosis, which massively enlarged the lower face, and destroyed all lip and cheek function bilaterally. All soft tissues below the zygomas and inferior orbital rims were replaced, with a substantial esthetic improvement.[61] As of late 2008, these initial experiences have been assessed favorably, a fourth facial CTA forming has been done by Maria Siemionow and co-workers in Cleveland.[62,63]

LARYNGOTRACHEAL TRANSPLANTATION

Kluyskens and Ringoir performed a laryngeal CTA in 1969 that was rejected at 8 months when immunosuppression was stopped for tumor recurrence, which progressed to fatality.[64] Early tracheal CTAs wrapped in omentum or muscle were also reported.[65–67] The first successful laryngotracheal CTA was by Strome and co-workers in Cleveland in 1988.[39] The recipient suffered traumatic laryngeal loss 20 years earlier. The entire larynx and adjacent tracheopharyngeal structures, including thyroid and parathyroid glands, were transplanted. Functional results and patient satisfaction have been excellent with restoration of normal swallowing and a normal sounding voice.[68–70] This landmark procedure established the basis for subsequent laryngotracheal CTAs.

This experience has been expanded substantially by Tintinago and co-workers in Medellin, Columbia, who had performed more than 18 clinical laryngotracheal CTAs by late 2007.[71–73] One of these also included the first esophageal CTA

as a component.[71] Tintinago et al report high-quality functional outcomes; over 70% of recipients achieved tracheostomy closure. Two grafts were lost to rejection, one of these due to nonavailability of immunosuppressive drugs.

The sum of these experiences makes laryngotracheal CTAs the most frequent indication outside the upper extremity. If future immunologic advances allow application after cancer resections, enormous applications await.

KNEE AND FEMUR TRANSPLANTATION

Among the earliest clinical cases, were vascularized CTAs of the knee, femur, and surrounding muscles pioneered in 1996 by Hofmann and co-workers in Munich, Germany.[36–38] Three were performed to address long segmental defects of the femur; 6 were total knee allografts. None of the grafts required skin, but a monitoring skin paddle was included in the most recent recipient.[74] All cases were initially successful, but none survived long term.[75] A thorough analysis of failure causes is needed before the promise of this CTA can be realized.

ABDOMINAL WALL TRANSPLANTATION

Abdominal wall CTAs based on the rectus abdominus myofasciocutaneous unit with a femoral/inferior epigastric vascular pedicle were introduced in 2003 by Levi, Tzakis, Selvaggi, and co-workers in Miami, Florida.[76,77] Many recipients had substantial loss of the abdominal domain, which left exposed visceral grafts. The recipients required immunosuppression for their simultaneous intestinal or multivisceral grafts; no alteration of that drug regimen was needed. Twelve abdominal wall CTAs were performed in Miami; 1 graft was redone after a technical failure. Three more abdominal wall CTAs have been constructed by Pinna and co-workers in Bologna, Italy, using microvascular techniques.[78,79] Excellent visceral coverage resulted for all recipients in both centers.

PERIPHERAL NERVE TRANSPLANTATION

Peripheral nerve CTAs have a long history, largely characterized by failure. Although some successes have been reported, they were poorly documented and not independently confirmed.[80] The most methodical, scientifically sound, clinical and basic science studies of nerve CTAs are being conducted by Mackinnon and co-workers in St. Louis. They have reported 7 clinical cases of long nerve CTAs: 2 were allografts only, and 5 mixed allografts and autografts.[81] Immunosuppression was only necessary for the 12 to 26-month period of axonal regeneration across the graft. Sensory, but not motor, effects returned across the 2 pure CTAs; sensory and motor return, across 3 mixed grafts. One CTA was rejected. Gruber et al reported a living donor mixed graft that failed to show any return.[82]

TONGUE TRANSPLANTATION

In 2003, a total tongue CTA was performed at the time of tongue carcinoma resection by Ewers and co-workers in Vienna, Austria.[83] Technical success was later followed by death from tumor recurrence.[69] This CTA holds promise for restoring a structure that is otherwise nearly unreconstructable, but this case reinforces need for extreme caution after cancer resections.

EXTERNAL EAR AND SCALP TRANSPLANTATION

In 2004, bilateral ears joined by a pedicle of cephalocervical scalp skin was transplanted by Hui and co-workers in Nanjing, China, for a recipient after surgical resection of advanced melanoma.[84] The tumor carried a poor prognosis. The initial technical success was followed by reports of the recipient's death.

PENIS TRANSPLANTATION

In September 2006, a penis CTA was done by Hu and co-workers in Guangzhou, China, after traumatic amputation.[85] The graft was initially successful restoring normal urination, but the recipient and wife experienced severe psychological stress postoperatively, and demanded elective removal after 2 weeks. This experience again reinforces the need for careful psychological screening.

UTERUS TRANSPLANTATION

In April 2000, a uterine CTA was done by Fageeh and co-workers in Saudi Arabia.[86] The graft was initially successful, but failed on the 99th day from suspected torsion and kinking of its vascular pedicle, requiring graft removal. Programs to repeat such CTAs have drawn extensive ethical concerns and discussions, with substantial cultural elements.[87]

DISCUSSION

The 2 branches of clinical allotransplantation began together just 50 years ago, with the seminal works of Peacock in composite tissue and Murray and co-workers in solid organs. However, these branches then diverged widely, as organ transplantation progressed dramatically and CTA virtually disappeared. In the 1990s, progress in immunosuppression brought about a composite tissue renaissance. Led by successful hand CTAs, the field expanded to over 10 graft types, including skin and epithelial-bearing structures. As of mid-2008, over 135 recipients have received over 150 CTAs.

A more fundamental difference transcends historic timelines—most solid organ grafts are life sustaining, whereas nearly all CTAs seek to enhance quality of life. This disparity creates substantially different risk–benefit calculations, indication judgments, and ethical considerations. Moreover, visible and emotionally laden grafts, such as hands and facial structures, carry issues of identity and psychologic adjustments. The field has evoked wonder, thoughtful analysis, and sharp controversy. Technical issues are being solved and immunologic management is improving, but issues of risks, indications, and ethics remain prominent, and will surely persist.

Vital to progress of CTA is progress in immunology. For example, in Louisville we have made major progress to avoid steroids and hope to achieve spaced weaning of antimetabolites. In the longer term, the quest for donor-specific tolerance through breakthrough discoveries, such as mixed allogenic chimerism, will likely lower CTA risks and cost substantially.[88–90] In turn, the current surge in CTA has enhanced support for basic immunologic research.[91] Breakthrough discoveries will surely determine the future of CTA, and its potential to dramatically change the field of reconstructive plastic surgery and related specialties. Moreover, such progress will likely affect solid organ transplantation in equally dramatic ways.

In conclusion, Composite tissue allotransplantation has a fascinating history of long quiescence until a recent renaissance of rapid progress and spectacular clinical applications. The mutual support between CTA and basic immunologic science creates a potential for breakthroughs that could dramatically transform the future of reconstructive surgery, transplantation surgery, and several related medical areas. The historic place of CTA in human medicine will ultimately depend on advances in the science of immunology.

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