

A new option for amputees: Transplantation of the hand

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Abstract—The permanent loss of a hand or limb results in significant challenges. A number of options are available to individuals who must deal with this loss, including reconstructive surgery using a person's own tissue to repair the damage or the use of prosthetic devices. We present an update on the most recent addition to the list of options, namely, composite tissue allotransplantation (CTA). In this procedure, tissue to repair the loss is taken from deceased donors who are giving hearts, kidneys, and tissue for transplantation. We report on the world's longest follow-up of CTA of the hand, as well as four other American hand transplant recipients. In very select patient populations, we propose that transplantation is now a clinical option for amputees.

Key words: amputation, amputee, composite tissue allotransplantation, CTA, function, hand, hand function, therapy, transplant, transplantation.

INTRODUCTION

The first hand transplant was attempted in 1964 in Ecuador [1]. The new hand, rejected by the patient's immune system, was amputated within 2 weeks. Since that time, all composite tissues of the hand, including skin, muscle, tendon, nerve, vessel, bone, and joint [2], have been individually transplanted with success in humans. Worldwide, 44 hand transplants have been performed (20 patients had one hand transplanted and 12 patients had both), for a total of 32 patients with a follow-up period ranging from 2 months to nearly 10 years (www.handregistry.com). Currently, our center based at

Kleinert, Kutz and Associates in Louisville, Kentucky, is the first program in the United States to have open enrollment in clinical trials of hand transplantation (see NCT00711373 at www.clinicaltrials.gov). Here we report an update on the five hand transplants performed at our center. We believe that the outcome of hand transplantation in these five patients represents current expectations of hand transplantation with respect to function, cosmetic appearance, and adverse events following transplantation.

PATIENT SUMMARIES

In the following sections, we describe each of five patients whom we have transplanted. We describe a brief history of each patient, why they were transplanted, the immunosuppression they received and complications they encountered, and a summary of how each patient is functioning with their new allograft.

Abbreviations: CMV = cytomegalovirus, CTA = composite tissue allotransplantation, ICU = intensive care unit, MMF = mycophenolate mofetil, MZL = marginal zone lymphoma, PTLTD = posttransplant lymphoproliferative disorder.

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Patient 1

- **History of injury:** Patient 1 is a 37-year-old white male who lost his dominant left hand in an accident with an M-80 firecracker in December 1985. His was a short transradial amputation. He is a paramedic instructor and wore an Otto-Bock myoelectric prosthesis for 13 years before receiving his new hand.
- **Past medical history:** Prior to his transplant, the patient was in good health. He was diagnosed with type 2 insulin-dependent diabetes in 1988 but was in otherwise excellent health.
- **Indications for transplant:** The short transradial amputation in this patient made him a good candidate for hand transplantation. Sufficient proximal muscles remained in his forearm to motor a functioning hand. The patient underwent a stringent screening and informed consent process. After careful consideration, he decided to proceed with the transplant. The hand transplant procedure was performed in January 1999. At this time, he has had his new hand for 10 years.
- **Immunosuppression induction regimen:** Presently, as with solid organ (i.e., heart or kidney) transplant recipients, patients who receive a composite tissue allotransplantation (CTA) must take drugs to suppress their immune system for the life of the graft. Patient 1 received the standard immunosuppression regimen of triple drug therapy—in his case, a combination of tacrolimus, mycophenolate mofetil (MMF), and prednisone. The patient did well on this regimen; however, in general, lower doses of immunosuppressive drugs mean less chance for complications. Therefore, at 8 years posttransplant, we weaned the patient off the steroids (prednisone). He is now being maintained on only tacrolimus and MMF. We are hoping that the patient will have fewer side effects because of this reduction in immunosuppression.
- **Relevant surgical details:** The transplant itself was uneventful. The patient recovered well and stayed in Louisville for the first 3 months after the operation. The patient underwent surgery in the third month after transplant for excision of the scar on his forearm. He also had some minor surgery to release some contractures in the new hand.
- **Rejection episodes and treatment:** This patient did have three episodes of rejection in the first year after the transplant, which were easily controlled with short courses of additional medication, most often with steroids. Notably, both tacrolimus and steroids can be

rubbed into the hand as a cream. With this approach, the drug is delivered directly to the skin of the transplanted hand, where it is needed.

- **Major complications:** This patient has had minimal medical issues since the transplant. The patient developed a viral infection common to transplant patients, cytomegalovirus (CMV), at 3 months; it responded to medication. He had an episode of right upper quadrant pain diagnosed with gallstones, elective laparoscopic cholecystectomy, and elective scar revision. He has managed his diabetes excellently, and his glycated hemoglobin levels are within normal ranges.
- **Function of transplanted hand:** All patients discussed in this article come to Louisville each year for an evaluation of their health and function. In Patient 1, motor function improved from the end of year 1 to year 6 and has remained relatively stable since (**Figures 1 and 2**). Interestingly, two-point discrimination (currently 5–6 mm, but variable) took 4 to 5 years to develop. Regarding function, even at 10 years posttransplant, this patient continues to experience sensory changes. The Carroll Test is a measure of function and activities of daily living. Patient 1's Carroll score at his 9-year annual evaluation was 73 out of a possible 99. He has full passive flexion and extension of the fingers. Grip and pinch strength decreased slightly at the 9-year evaluation. At the 10-year evaluation, his overall function was very similar to that at his 9-year evaluation. One change from year 9 to year 10 was his ability to feel a feather in the areas between his fingers.



Figure 1.
Patient 1 at 4 years posttransplant.

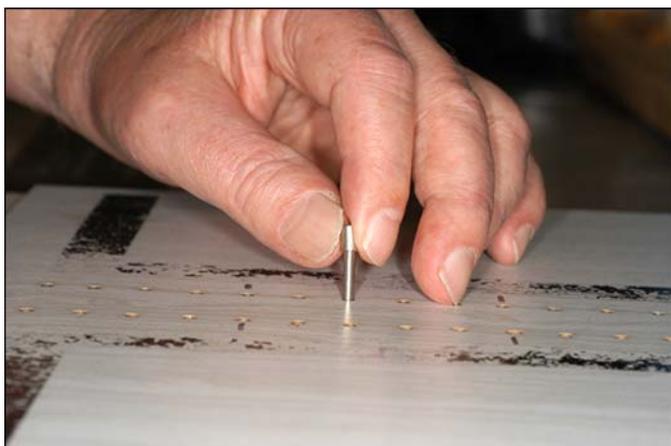


Figure 2.
Patient 1 at 7 years posttransplant.

We are surprised that he continues to have sensory changes, even 10 years posttransplant. He can feel hot and cold, as well as rough and smooth textures. He is able to toss and catch a ball, turn the pages of the newspaper, unscrew the cap on a water bottle, pick up small objects, and independently complete all activities of daily living. Annual psychosocial evaluations find this patient experiencing great satisfaction and happiness with his transplant.

Patient 2

- **History of injury:** This 36-year-old white male lost his nondominant left hand in a fireworks accident in 1996.
- **Past medical history:** Patient 2 had no health issues. He wore a cable hook prosthesis and worked full-time prior to his transplant.
- **Indications for transplant:** He had a short transradial amputation and successfully underwent hand transplantation in February 2001.
- **Immunosuppression induction regimen:** Patient 2 received an induction regimen similar to Patient 1. He received Simulect[®], an antibody to the interleukin-2 soluble receptor as an induction agent, as well as standard triple drug immunosuppression therapy based on tacrolimus, MMF, and prednisone. Within a few weeks of transplant, this patient developed high blood sugar levels that were difficult to control, related to the high tacrolimus levels and the multiple steroid bolus regimens to treat rejection in the weeks following the transplant. To improve blood sugar control, we discontinued MMF and instead administered rapamycin,

another type of immunosuppressant. The patient still requires monitoring of his blood sugar and takes medication to regulate levels. He does not require insulin. Late in the posttransplant course, Patient 2 was successfully weaned off steroids (prednisone); he is currently maintained on only two types of immunosuppressive drugs (tacrolimus and rapamycin).

- **Relevant surgical details:** The transplant went very well. The patient had preoperative treatment of a third-degree acromioclavicular joint separation about 6 months before the transplant. The transplant surgery was uneventful.
- **Rejection episodes and treatment:** This patient had five episodes of acute rejection in the first year, with one episode treated with a strong anti-rejection medication, antithymocyte globulin. In years 5 and 7 posttransplant, he had other episodes of rejection related to noncompliance with medications. The rejections responded to treatment and resuming compliance with his medication.
- **Major complications:** The two major complications in this patient were the development of high blood sugar/diabetes following transplant, and osteonecrosis of the hip. Both of these complications are directly related to the prednisone and/or tacrolimus. This patient developed osteonecrosis of both hips (one side in year 2 and one side in year 6 posttransplant), which required total hip replacement on both sides. In response to this issue, we implemented a steroid-sparing induction regimen using Alemtuzumab (Campath[™] 1H) in our subsequent three patients. This steroid-sparing induction regimen is now routinely used in kidney transplantation [3–4]. We also weaned Patient 2 off systemic steroids in year 7 posttransplant. We are hopeful that this reduction in the use of steroids will result in fewer complications in this patient and future patients.
- **Function of transplanted hand:** This patient achieved a level of fair function at the 1-year evaluation, but in contrast to Patient 1, he has not improved over the years with respect to intrinsic muscle function. His Carroll Test at his first annual evaluation was 52; it has improved only marginally to 57 in 7 years. The range of motion in the forearm is good but only 40 percent of normal in the wrist. Tightness in the ligaments of the hand persists, even at 7 years. Sensory return has been significantly less than Patient 1; however, he has not had a problem with ulcers on the transplanted hand,

suggesting sufficient protective sensation. Touch localization (to tips of thumb; long, ring and small finger) is poorly developed, but temperature and vibration sensation (256 cps) have returned. Patient 2 does not have two-point discrimination. He can detect the stimulus but cannot discriminate. He has a strong lateral pinch that allows him to pick up and grip objects. He can toss and catch a ball, turn the pages of the newspaper, unscrew the cap on a water bottle, pick up small objects, tie his shoes, and complete all activities of daily living, although with a different technique than he uses with his right hand. He owns and operates a gutter installation business and actively uses the hand in his work (**Figures 3 and 4**). At his 7-year annual visit, he had a callus on the transplanted hand from using it in his business to steady sheets of aluminum as they are cut.

Patient 3

- History of injury: This 54-year-old white male underwent amputation of his dominant right hand 34 years ago after an industrial press accident.
- Indications for transplant: His amputation was a short transradial loss. The transplant was performed in November 2006.
- Past medical history: Patient 3 functioned well with a cable hook prosthesis. No health issues were present.
- Immunosuppression induction regimen: This patient received the new type of steroid-sparing immunosuppression induction treatment (Campath 1H) that is



Figure 3.
Patient 2 at 6 years posttransplant.

designed to use only two types of immunosuppression from the beginning. We never started this patient on steroids (prednisone); he is maintained on tacrolimus and MMF. He is the first hand transplant patient to have successfully avoided prednisone maintenance.

- Relevant surgical details: The transplant went well, with no unexpected events. About 2 weeks after the transplant, the patient developed a seroma on the ulnar forearm that was debrided and grafted with skin from the patient's thigh. This healed with no further issues (**Figure 5**).
- Rejection episodes and treatment: Patient 3 has had three significant rejection episodes in the 2 years following



Figure 4.
Patient 2 at 6 years posttransplant.



Figure 5.
Patient 3 at 4 months posttransplant.

his transplant. The first was a period of combined rejection and infection (CMV viral infection) about 2 months after the transplant. The rejection he had at the time of infection resolved completely with a treatment of topical agents only (topical tacrolimus and topical steroids). A second episode of rash and swelling occurred about 18 months after the transplant. We transiently increased his immunosuppression, and the swelling resolved in about 1 month. Interestingly, hand function does not seem to be affected by rash or swelling in the skin. Finally, Patient 3 has had a recent episode of rejection in response to decreasing immunosuppression as a part of a treatment for a complication. This latest rejection resolved once immunosuppression was restored.

- Major complications: This patient had an episode of CMV infection concurrent with a rejection episode, about 2 months after the transplant. The other major complication noted in this patient was an unusual B-cell clone in the blood that was identified 23 months posttransplant. At that time, we also identified a monoclonal T-cell clone. These clones were identified during the course of routine laboratory blood testing. The patient has no symptoms, positron emission tomography and computed tomography scans were negative, and marrow biopsy showed a small involvement of both clones. The initial diagnosis was posttransplant lymphoproliferative disorder (PTLD), and the patient was sent home on reduced tacrolimus, with a discontinuation of MMF. The laboratory blood testing was repeated and reviewed by a number of experts. We saw no significant changes in the absolute number of clones following the reduction or resumption of immunosuppression. Presently, we have a differential diagnosis of either PTLD, marginal zone lymphoma (MZL), or aberrant clones of unknown origin. The World Health Organization histological classification is MZL. This is the most likely diagnosis and would not be related to the transplant. The patient continues to be asymptomatic, and we continue to follow him closely.
- Function of transplanted hand: At the 2-year evaluation, Patient 3's function in the transplanted hand measured fair on the Carroll Test (57 of a possible 99). The range of motion was improved, with active digit motion reaching approximately 45 percent of normal (**Figures 6 and 7**). Sensory evaluation showed advancement of sensation, with diminished protective



Figure 6.
Patient 3 making fist at 1 year posttransplant.



Figure 7.
Patient 3 extending hand/arm at 1 year posttransplant.

function and light touch localization in the index, ring, and small fingers only. He does not have two-point discrimination. He can detect the stimulus but cannot discriminate. He can feel cold and heat. While the Carroll Test does not indicate significant improvement over his prosthesis, this test does not take into account the ability to feel touch, heat, or cold. He simply could not perform a number of tasks with his prosthetic, such as turning a door knob or riding a snowmobile. Since the 1-year annual evaluation, he can now perform a number of new tasks, including turning the key in his car's ignition, stabilizing power tools, pouring from the cereal box and coffee pot, brushing his teeth, and picking up coins from his other hand. Additionally, when asked what task was most important to him, Patient 3 responded that he can now hug his wife with two hands and he can cheer at a baseball game without inadvertently clubbing the fan

beside him with his prosthetic. The joy he experiences at being able to do these small things is not reflected in a Carroll Test.

Patient 4

- History of injury: This 32-year-old white male underwent amputation of his dominant right hand following a firearm accident in 2002.
- Past medical history: Patient 4 functioned well with a cable hook prosthesis. No health issues were present.
- Indications for transplant. He had a short transradial amputation. The transplant was performed in July 2008.
- Immunosuppression induction regimen: Like Patient 3, this patient received the steroid-sparing Campath 1H induction regimen. We never started this patient on systemic steroids (prednisone). He is maintained on a double therapy of tacrolimus and MMF.
- Relevant surgical details: The surgery went well, lasting approximately 14 hours. The patient was admitted to the intensive care unit (ICU) postoperatively for mild hypotension and pulmonary congestion. These conditions quickly resolved and he was transferred out of ICU and onto a regular postoperative floor.
- Rejection episodes and treatment: This patient has had a very quiet clinical course with respect to rejection. Presently, he is only 6 months posttransplant; however, he has not had a severe rejection episode to date. He has had three episodes of rash or slight swelling, all of which responded to topical creams of tacrolimus and clobetasol.



Figure 8.
Patient 4 with supination of transplanted hand at 1 month.

- Major complications: At this time, Patient 4 has had no major complications; however, it is still early in the posttransplant period. (See note in next section.)
- Function of transplanted hand: All patients receive therapy 5 to 6 days a week posttransplant. At 4 weeks posttransplant, Patient 4 could supinate (**Figure 8**) and pronate (**Figure 9**) the hand and, with support, pick up light objects with the thumb and forefinger (**Figure 10**). His function improved rapidly, and by 3 months posttransplant, his Carroll score was 67, equivalent to Patient 1 at 5 years posttransplant. Patient 4 continues to do well and receives therapy near his hometown. We continue to monitor his progress.



Figure 9.
Patient 4 with pronation of transplanted hand at 1 month.

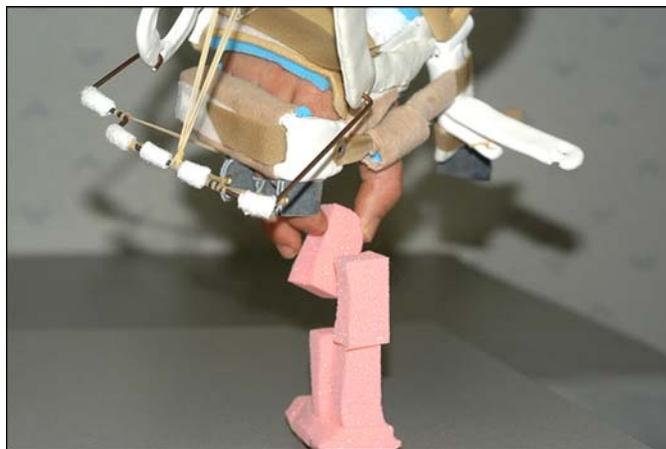


Figure 10.
Patient 4 stacking objects at day 26 posttransplant.

(Note: At the time of publication, this patient had a serious adverse event. He had unmanageable ischemia in the hand, resulting in amputation at 9 months post-transplant. Early analysis indicates that this was secondary to severe chronic rejection restricted to the arteries of the allograft. We are preparing a separate manuscript to report this event.)

Patient 5

Patient 5 received a hand transplant in late November 2008. Because the transplant was so recent, we have limited information on this patient. He is a 43-year-old white male who lost his hand in a foundry accident in 2006. He too had a short transradial amputation. This patient also received the Campath 1H induction regimen and is being maintained on tacrolimus and MMF. He had one rejection episode that resolved quickly. At this very early stage in the posttransplant course, the patient is doing well and regaining function.

DISCUSSION

After the failure of that first attempted hand transplantation in 1964, work on CTA was discouraged for decades. More than 30 years later, hand transplantation at

our Louisville center began, following protocols for solid organ transplantation in addition to extensive research [5–9]. Continual follow-up on our current patients not only maintains their CTA survival but also builds on our previous research, updating and improving all aspects of the transplantation process, from patient selection to postoperative care (**Table**) [10–11]. Multiple conclusions have been reached that pertain to the Louisville cases.

CONCLUSIONS

First, it is possible to achieve prolonged survival of a transplanted hand using the same kind of drugs that are used in kidney transplant recipients. In fact, we are able to maintain hand recipients on only two drugs, and we continue to research ways to further reduce the amount of immunosuppression needed.

Second, reasonable function does return. We were worried that our patients might injure their hands while they were waiting for protective sensation to return, but that has not been the case. None of our patients developed ulcers or chronic injuries at any time during sensory recovery. As demonstrated by Patient 1, good return of intrinsic muscle function can occur; this type of function

Table.

Summary of Louisville composite tissue allotransplantation hand recipients.

Patient	Time After Tx	Immunosuppression Regimen*	Severe Rejection Episodes	Complications	Two-Point Discrimination	Function
1	10 yr	Simulect®, tacrolimus, MMF, prednisone	3 (all in first year)	CMV	Yes	Intrinsic muscle recovery; continues to improve
2	8 yr	Simulect®, tacrolimus, MMF, prednisone	7	Diabetes; osteonecrosis of hips	No	Good function; no intrinsic
3	2 yr	Campath® 1H (tacrolimus, MMF)	3	CMV, MZL	No	Good function; no intrinsic yet
4	6 mo [†]	Campath® 1H (tacrolimus, MMF)	0	Chronic rejection—9 months	Yes	Excellent
5	2 mo	Campath® 1H (tacrolimus, MMF)	0	—	Too early	Good early progress

*First two patients were weaned off prednisone late posttransplant. Patients 3 to 5 have never used systemic prednisone.

[†]At the time of publication, this patient experienced severe ischemia of the hand, resulting in amputation of the new allograft at 9 months posttransplant.

CMV = cytomegalovirus, MMF = mycophenolate mofetil, MZL = marginal zone lymphoma, Tx = transplantation.

allows one to pinch the fingers and thumb together. Patients 1 and 2 eventually demonstrated hand function superior to that obtained with a prosthesis, and all information indicates that the same will be true for Patients 3 and 4. All our patients were discharged to home and work in an anticlaw splint 3 months after surgery. All have returned to full-time work. Patient 2 has returned to a position that involves some manual labor, and his new hand is allowing him to function well.

Third, as in solid organ transplants, the rejection that did occur was managed with medication. At the time of submission, we had not seen evidence of chronic rejection in any of our patients. However, we now know that arteriopathy can occur in hand transplant patients.

Fourth, we have observed potentially life-shortening complications such as hypercholesterolemia, diabetes, and hypertension in our patients. Now we have found a possible lymphoma in Patient 3, and we are following him to determine whether this lymphoma is related to the transplant. Regardless, PTLD is a very real risk of transplantation, one that any potential hand transplant recipient should carefully consider. We also noted major complications, such as avascular necrosis of the hips in Patient 2. We acted on this information, aggressively reducing the maintenance immunosuppression, and have now successfully eliminated maintenance steroid use. Another short-term goal we have is monotherapy immunosuppression, with donor-specific tolerance as a long-term goal.

The osteonecrosis in Patient 2 that required left and right hip arthroplasty was most likely caused by prednisone maintenance and steroid boluses used to treat early rejection. This, in addition to the other risks linked to steroids (hyperlipidemia, diabetes, and hypertension), prompted us to implement steroid-sparing protocols. We have demonstrated that severe rejection will resolve and can be treated with topical tacrolimus and steroids alone, further reducing the need for systemic medication and, thus, the associated complications. The functional capabilities to date of Patients 1 and 3 have exceeded our expectations. All three patients scored fair at their 1-year evaluations, displaying function superior to their respective prostheses. Patients 1 and 2 have demonstrated improvement in function and strength in subsequent annual evaluations. Patient 1 continued to see improvement as posttransplant years progressed. At his 9-year evaluation, Patient 1 received the high Carroll score of 72. In contrast, Patient 2 received a Carroll score of 57 at his 7-year evaluation, showing only marginal improve-

ment since his first year posttransplant. However, Patient 2 also continues to show sensory improvement. Patient 3, an amputee for over 30 years before his transplantation, had an extraordinarily high preoperative Carroll score; at his 1-year evaluation, he achieved the same score of 56. Presently, it is too early to evaluate the long-term function in Patients 4 and 5. However, at 3 months Patient 4 has achieved a Carroll score similar to that of Patient 1 at 5 years. Thus, we are hopeful that he will regain intrinsic function quickly. Differences in functional recovery between the patients are likely due to variations in patient compliance, as well as amounts and degrees of rejection episodes. Regardless of the differences in these cases, most important is that the CTAs of Patients 1 to 3 in the study are functioning at 10, 8, and 2 years, respectively. While every recipient receives varying degrees of benefits, these patients have function and sensation of the hand that they could not achieve with a prosthesis. This success is not measured by a Carroll Test. We are optimistic that Patients 4 and 5 will enjoy similar success with their transplanted hands.

All five of our patients use their new hands in daily activities. Some of the activities Patients 1 to 4 can now perform are listed in **Figure 11**.

In Patient 1, transplantation allowed an important sense of reparation to occur, providing relief from guilt about the accident that had led to amputation. Patient 1 was delighted with his new hand. His body image improved significantly, and he reported increased confidence, feeling “whole” and “balanced.” Patient 1 was

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|---|
| <p>Open regular door knobs.
 Pick up smaller objects, checkers, washers, small nuts, and bolts.
 Lift gallon of milk or water from refrigerator.
 Hold steering wheel with transplanted hand only.
 Use wrench and other tools.
 Use rake and other garden tools.
 Take change in palm.
 Use fork and knife.
 Swing golf club or baseball bat.
 Catch balls.
 Tie shoes.
 Assist in holding dishes and food items in buffet line.</p> |
|---|

Figure 11.

Activities of daily living performed in five U.S. hand transplant patients.

diabetic prior to the transplant, but has managed his condition well, even after 10 years of systemic immunosuppression. This suggests that, to date, his immunosuppression regimen has not significantly affected his diabetes. In the early posttransplant phase, we treated Patient 2 for mild mood and sleep symptoms secondary to steroids. At 1 year posttransplant, Patient 2 experienced situational depressive symptoms that also responded to treatment. At 2 years posttransplant, Patient 2 remained satisfied with the transplant and felt it had met his goals. He reported feeling increased personal confidence. At 2-1/2 years posttransplant, in the context of hip osteonecrosis and psychosocial stresses, Patient 2 experienced a return of depressive symptoms and some associated decrease in medical compliance, but his mood and medical compliance improved as the stress decreased. Following his second hip replacement in May 2007, Patient 2 is back at work and has been demonstrating good compliance with immunosuppression medication. He has been weaned from prednisone and continues to function well, reporting an excellent quality of life at 7 years posttransplant. Patient 2 experienced major transplant-associated complications with the hip replacements but, despite these, states that he does not regret his hand transplant. Patient 3, at 2 years posttransplant, is doing very well. He is satisfied with his hand function, with the exception of his thumb, which does not yet have pinch function. In addition, he does not care for the hair pattern on the transplanted hand, but has accepted it. At this time, we are closely monitoring Patient 3 with respect to his lymphoma. The most likely diagnosis is MZL, but PTLD has not been completely ruled out. The diagnosis can only be completely differentiated with time. Patients 4 and 5 are very early in their posttransplant courses, but both are doing well. All five patients have accepted their donor hands and see them as their own. (Note: At the time of publication, our fourth patient had an acute ischemic event that resulted in amputation of the hand at 9 months posttransplant. Our early investigations suggest this was due to very aggressive chronic rejection directed at the arterial tree, resulting in massive intimal hyperplasia. This event was in the absence of donor-specific antibodies and following a quiet clinical course with respect to acute rejection. We are continuing to investigate this event and have a separate manuscript in preparation. The patient tolerated the surgery well and is at home. We are in the process of revising our protocols to add additional

tests to monitor for chronic rejection and severe intimal hyperplasia.)

Our intermediate long-term results of hand transplants have demonstrated functional return similar to that of replants [12]. CTA survival and quality of life after hand transplantation have far exceeded initial expectations. We conclude that allogeneic hand transplant is not only feasible but also an option for very select patients and highly specialized centers with the infrastructure and experience in CTA and organ transplantation.

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Author Contributions:

Study concept and design: C. L. Kaufman, W. B. Breidenbach.

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Analysis and interpretation of data: C. L. Kaufman, B. Blair, W. B. Breidenbach.

Drafting of manuscript: E. Murphy.

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