

Hand Transplantation:

Current Status

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Abstract

The hand is a very special organ, with unique functions and versatility in the human body. Our hands are pivotal in manipulating our environment, receiving feedback from our surroundings and communicating our unspoken words by gestures. Thus, the loss of a hand is a tragic, disfiguring event with profound personal, vocational, financial and social implications. Transplantation of life-saving solid organs is now widely accepted in both the medical and lay communities. The technical skills and prerequisites for hand transplantation have been honed over recent decades, culminating in the recent commencement of hand transplantation in several centers around the world. However, unlike life-saving solid organ transplantation, hand transplantation has been greeted with less enthusiasm in the professional community because it is not yet clear what the long-term risks-to-benefits ratio is. The scientific background, and the potential risks, benefits, and ethical aspects of this procedure are discussed. Successful transplantation to amputees of fully integrated and functional hands is a worthy goal. Hopefully, at some point in the future, hand transplantation will become another safe and viable option for amputees to consider.

Key Words: Transplant, ethics, hand, hand transplant.

THE HAND IS A VERY SPECIAL ORGAN. Its level of function and versatility is unique, in that it requires an integration of sensory input and fine motor control not found anywhere else in the body. The sensibility of the hand is vital. It is disproportionately represented in the brain, indicating the degree of its importance. Our hands are pivotal in manipulating our environment, receiving feedback from our surroundings and communicating our unspoken words by gestures. The hands have even been credited with being intimately involved in the development of language (1–3).

The loss of a hand is a tragedy; it is profoundly disfiguring, both physically and psy-

chologically. The hand is an external organ that carries obvious emotional investment; people do not pine for the loss of a kidney as they do for the loss of a hand. For some, the loss of a hand represents the end of a vocation, for most it represents a reduction in their ability to support themselves and their families, and for all there is a profound distortion in their perceived personal body image. Successful transplantation of fully integrated and functional hands to amputees is a worthy goal. Hopefully, at some point in the future, hand transplantation will become another safe and viable option for amputees to consider.

Being a composite of multiple tissue types (including bone marrow) with differential immunogenicity, the hand differs significantly from traditionally transplanted solid organs, which have a relatively homogeneous parenchyma. The most significant difference, however, is that hand transplants are not life-saving procedures. At best they may improve the recipients' quality of life, although some would argue this point. Unlike solid organ transplant recipients, amputees already have a range of optional prosthetic devices (aesthetic and functional) that can improve the quality

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of their lives without being potentially life threatening.

Whereas transplanted organs perform their specific physiological tasks without nervous integration, a transplanted hand needs to achieve cortical representation for both sensibility and fine motor control. Solid organ transplants continue to function “optimally” whether the recipient is aware of them or not. To be of value, however, hand transplants require the continual activity and consciousness of the recipient.

Although hand transplantation is not a life-saving procedure, Moore’s six criteria for assessing the ethical appropriateness of this innovative surgery are still relevant (4). According to Moore, transplantation is an ethically acceptable medical option only when all of these standards are met:

1. The scientific background of the innovation.
2. The skill and experience of the team.
3. The ethical climate of the institution.
4. Open display.
5. Public evaluation.
6. Public and professional discussion.

In our opinion, the first modern-era hand transplant, performed in 1998, failed to fulfill some of these criteria, particularly those of open display and public evaluation (5). Most commentators accept that the Louisville group, which performed the second hand transplant in 1998, met the latter five of Moore’s standards (6). Only the scientific background of the innovation remains in question. Siegler (7) wrote, “the question is whether the equipoise consideration has been satisfied. Equipoise describes a situation of uncertainty in which the clinical investigator regards the potential outcome of an experiment or clinical trial as truly balanced between its potential for benefitting the patient or for causing unintended harms.” Do we know enough about the potential risks and benefits of human hand transplantation to satisfy the question of equipoise? Needless to say, the true long-term risks and benefits that can be anticipated from this surgery are not known. We can, however, extrapolate from our experience with hand replantation, with a limited number of other non-solid organ allogenic transplants, and with traditional organ transplantation and animal limb/composite tissue transplant experimentation, to meaningfully discuss the likely results.

Relevant Experience

Malt performed the first upper extremity replantation at the Massachusetts General Hospi-

tal in 1962 (8). Shortly thereafter, Chen performed the first microsurgical hand replant (9). A successful hand replant depends upon the level of amputation, maximizing tissue survival and restoration of function, i.e., “survival without restoration of function is not success” (10). Given that hand transplants will be performed in dedicated hand centers upon surgically amputated tissues (devoid of crush or avulsive injury), it is likely that initial revascularization, and hence tissue survival, will be successful (rejection issues will be discussed later). Outcome scoring systems for limb replantation have been applied to several case series reviews of replantations at the wrist or distal forearm (11). Good-to-excellent results occurred in 23–89% of the patients reported in five series with more than 10 patients. The more proximal the replantation, the worse the result that can be anticipated; fingertip replants do very well (12, 13). At the distal forearm level, two-point discrimination return is usually greater than 30 mm and most patients do not have protective sensation (14). Active range of motion is incomplete, about 28–38% of normal, and regaining intrinsic muscle function is the exception, not the rule (14). In our personal experience, every patient who had an immediate forearm amputation has returned to work, whereas everyone with forearm replantation has failed to return to work.

The advantages of planned execution (ideal circumstances for tissue transportation and cooling, pristine donor tissues, etc.) for initial limb revascularization may be offset by the recipient limb’s loss of functional outcome secondary to chronic scarring, muscle atrophy and/or contraction. Additional unknown factors are the effects of immunosuppression and episodes of rejection (acute or chronic) upon functional outcome. It is reasonable to assume that the results of allogenic hand transplantation will be, at best, equivalent to the results of hand replantation (11).

There have been scattered reports of composite tissue allogenic transplantations in humans. Jones et al. (15) reported on the successful transplantation of a rectus abdominis muscle for scalp reconstruction in a renal transplant recipient, Guimberteau et al. (16) reported two cases of transplanted digital flexor tendon/tendon sheath complexes, and Hofmann et al. (17) reported on vascularized allogenic femoral diaphyseal and knee joint transplants (2 of 5 requiring removal for chronic rejection). Strome has transplanted a larynx (18). None of these

composite tissue allogenic transplants included skin, a highly antigenic tissue that has repeatedly proven troublesome in animal experiments. The long-term results of these procedures are still unknown. Interestingly, immunosuppression was only given for six months to those patients with digital flexor tendon/tendon sheath transplants, and there have been no negative sequelae during the following six months, in which immunosuppression was not administered.

The results of animal experiments with allogenic limb transplants and composite tissue allogenic transplants are usually divided into small animal and large animal/primate groupings. Without immunosuppression, limb and composite tissue allogenic transplants are doomed to rejection, and most of the literature is devoted to trials of alternative immunosuppression regimes. Lee et al. (19) have shown that a different degree of antigenicity is present in the various components of a composite tissue graft. Additionally, the host immune mechanism responds to the different antigenic stimuli differently (e.g., muscle causes a greater cell-mediated response and skin a greater humeral response). Thus, it is likely that any successful immunosuppression regime will need at least two agents.

Cyclosporin has been extensively studied in the rodent model. Rejection-free survival of more than one year has been reported with cyclosporin alone (20). This was at the expense of high doses (8 mg/kg/day), and hence, there was associated morbidity. Other cyclosporin-only experiments have failed to replicate these results. Even with higher doses (15–25 mg/kg/day), early rejection was a problem. The outcomes of two rodent limb allograft experiments using FK-506 for immunosuppression also demonstrated longer-term survival at the cost of significant morbidity, primarily *Pneumocystis carinii* pneumonia (suggesting the development of graft-versus-host disease) and/or chronic mild-to-moderate signs of skin rejection (21).

Mycophenolate mofetil (MMF, RS-61443) successfully prevented rejection for 32 weeks in 5 of 6 rats with whole limb transplants. This group displayed restoration of sensory and motor function (22). MMF was then combined with low-dose cyclosporin, leading to 89% survival at 230 or more days (23). On this basis, combination therapy with low-dose cyclosporin and MMF has been proposed as an appropriate immunosuppression regime for allogenic transplantation.

Lance et al., using antilymphocyte serum, azathioprine and hydrocortisone combinations, and Goldwyn et al., using 6-mercaptopurine and azathioprine in canine hind limb allogenic transplant experiments, failed to demonstrate immune tolerance without significant drug toxicity (24, 25).

Three studies using primate models, which more closely resemble the human immune system and anatomy, have been published (26–28). Daniel et al. (26) transplanted four baboon hands and seven neurovascular-composite-tissue, digital-free flaps, using high-dose cyclosporin (trough levels > 1000 ng/mL) and methylprednisolone (4.4 mg daily) for maintenance immunosuppression. One hand remained in excellent condition 300 days after transplantation. The remaining three underwent various degrees of rejection: one was hyperacute, one was salvaged at two months from a severe rejection episode, and the fourth hand was lost secondary to an iatrogenic reduction in the cyclosporin maintenance dose followed by an infection. Electrophysiologic testing of the two long-term surviving hands showed motor, sensory and nerve regeneration. All seven composite digital flaps were technically successful; however, the first three showed signs of rejection, including edema, vesiculation, ulceration and epidermal sloughing.

Stark et al. also used a baboon model for the transplantation of eight hands, with cyclosporin (trough > 800 ng/mL) and prednisolone (5 mg daily) for immunosuppression (27). Six of the hands were lost in the first 15 days. Loss of the first hand, at two days, may have been due to a technical error, but the remaining five showed signs of acute rejection. The seventh hand was lost due to an anesthetic problem. The eighth hand survived 296 days before elective sacrifice; throughout this period there was evidence of chronic skin rejection. Of note were the findings of patchy lymphoplasmacellular infiltrates in specimens of the recipient's autologous tissue. The authors felt that these may have represented discrete areas of graft-versus-host disease and warranted further investigation.

The final study, by Hovius et al. (28) and Stevens et al. (29), reports using a Rhesus monkey partial-hand transplant model. Cyclosporin (25 mg/kg/day) and prednisone (1 mg/kg/day) maintenance immunosuppression was used. Acute rejection episodes were treated by either steroid dose increases or monoclonal antibodies specific for different surface antigens on immunocompetent cells. Ten of the 12 recipients

had histologically confirmed rejection. In all cases, the skin was more rapidly rejected than were nerve and muscle. Rejection could not be reversed by increasing the steroid dose. Two of the five cases of rejection treated by monoclonal antibodies were successfully reversed on two occasions each. Significant immunosuppression side effects were encountered. One monkey died from irreversible shock after the first injection of monoclonal antibodies, three died from bacterial infections and three others died from lymphoid tumors. Additionally, autopsy revealed that one of the monkeys that died of sepsis also had a tumor. There was no correlation between cyclosporin trough levels and death by either sepsis or lymphoid tumor. The authors concluded that "a more effective, less toxic immunosuppressive regime is needed before actual allogeneic transplantation of the hand should be performed in human patients, though it was demonstrated previously that it is technically feasible and that results for functional recovery are promising" (28).

Of particular interest are the two reports of porcine limb transplantation by Ustuner et al. (30) and Jones et al. (31), both using a radial forearm osteomyocutaneous flap model. The first study used cyclosporin (trough levels 100–300 ng/mL), MMF (500 mg daily), and prednisone (0.1 mg/kg daily) immunosuppression. Of the ten successful procedures, one pig died from pneumonia (day 19) and another from an anesthetic complication (day 30); neither pig had any signs of rejection. Two flaps were lost from severe rejection on days 25 and 29, respectively. Three flaps had mild-to-moderate rejection at day 90 (the study end point). The remaining three flaps were free of rejection at day 90, two of them having had an earlier episode of spontaneously resolving rejection. During the trial, two of the pigs developed pneumonia and one developed a wound infection. There were also two episodes of distant septic arthritis. The second porcine study (from the same group) used tacrolimus (FK-506, trough levels 3–8 ng/mL), MMF (500 mg daily), and prednisone (0.1 mg/kg daily) for immunosuppression. Three of the pigs died from pneumonia on days 29, 30, and 83. Four of the pigs developed early grade I-III rejection; three of these resolved, but the fourth died prior to healing from a gastric rupture on day 42.

Combining these two studies reveals that only 11 of 19 (58%) transplants survived the experiments, and that the mortality rate was

32% overall. None of the viable transplant recipients completed the experiment without at least one episode of rejection or sepsis. Later, in a paper reporting the first-year follow-up of their first hand transplant, Jones et al. state, with particular reference to these porcine experiments: "In these studies, however, drug doses were not adjusted according to the clinical progress of the animals, as would be done when humans are treated. Therefore, our decision to proceed with the tacrolimus-based regime for immunosuppression after human hand transplantation was based on the hypothesis that efficacy in preventing rejection and systemic toxicity could be balanced clinically" (6).

The consensus at the conclusion of a 1997 international symposium on composite tissue allotransplantation was that it was time to "just do it" (32). On Sept. 23, 1998, the distal right forearm of a 41-year-old donor was transplanted to a 48-year-old man in Lyon, France (5). Four months later, the first successful American hand transplantation was completed by the Louisville team (6). To date, fourteen hand transplants in eleven patients have been performed over the past three years (33). The first of these fourteen transplants was amputated for chronic rejection at 2 years and 4 months. The longest surviving transplant is now more than 3 years post surgery.

The initial functional outcomes of the first four human hand transplants have been published (34). The time to follow-up ranged from 8–20 months. Only the range of motion of the forearm and wrist is documented, but the results are better than would have been expected based on previous results of replantation of the hand and wrist. There has been electromyographic evidence of reinnervation of the intrinsic muscles of the hand. Sensory return, however, has been less than expected. Although all 4 patients showed progression of an advancing Tinel sign, Semmes-Weinstein sensory testing varied from between deep pressure sensation to loss of protective sensation to diminished protection sensation. Finally, the Carroll test of functional recovery (35), which integrates mobility, motor function, and sensation, was available for 3 of the 4 patients and ranged between 52 and 75, which translates to 1 good and 2 fair results.

The first American recipient has been able to return to work as a paramedic and perform duties he was previously incapable of, even with a prosthesis. A one-year follow-up paper has documented that (6):

1. he required anti-rejection intervention 3 times in the first 30 weeks,
2. he developed tissue-invasive cytomegalovirus infection at 15 weeks,
3. there is electromyographic evidence of innervation of the intrinsic muscles,
4. temperature, pain and pressure sensation is present in the fingers (no formal assessments were reported).

In an editorial in the *New England Journal of Medicine* (36), Herndon suggested that hand transplantations will most likely continue to be performed while we await the results of the procedures that were already performed. More basic research and safer immunosuppressive drugs are still needed. He poses the basic question about hand transplantation (36): "Should they be?" His suggestion, with which these authors agree, is to limit the procedure to patients who have lost both hands or who are already on immunosuppressive drugs for other reasons.

Additional Considerations

Lee and Mathes classify the risks associated with chronic immunosuppression into three categories: adverse effects of individual immunosuppressants, opportunistic infections and malignancy (11). The first French and American patients have all been prescribed tacrolimus, MMF and prednisone for their long-term immunosuppression. These drugs are not without dose-related risks, including nephrotoxicity, neurotoxicity, diabetogenicity, osteoporosis, bone marrow suppression and gastrointestinal toxicity. Historically, more than 80% of organ transplant recipients develop at least one infection after transplantation, and 40% of the deaths are due to infectious complications occurring alone or following rejection (11). The risk of malignancy associated with chronic immunosuppression in organ transplant recipients has been reported in the range of 4–18%. The incidence of malignancy relates both to the duration and extent of the immunosuppression.

In some of the animal experiments, there was evidence that a chimeric state had developed, in which functional immune components of both organisms coexisted, in a few of the more successful recipient-donor pairings. While this privileged state is beneficial when it occurs, the transplantation of immunocompetent T lymphocytes into an immunosuppressed recipient risks the development of graft-versus-host disease (GVHD). GVHD is the major com-

plication of bone marrow transplantation and, as such, is a definite possibility with allogeneic hand transplants. In broad terms, GVHD can be prevented by decreasing the number of donor T cells transplanted or by immunosuppressing the recipient after the transplant. As described above, the immunosuppressive regimes tested may have been insufficient to prevent the occurrence of GVHD despite significant recipient immunosuppression side effects.

Conclusions

Questions remain about the adequacy of the scientific background to human hand transplantation, particularly with regard to:

- what constitutes appropriate immunosuppression,
- the likelihood of infections,
- the possibility of malignancy and graft-versus-host disease,
- the likelihood of a fair-to-poor functional result of 11–76%,
- the lack of long-term successful animal transplantation without evidence of chronic rejection or systemic toxicity.

We believe that without more substantive evidence of an expectation for a good outcome, the procedure should be limited to patients who have lost both hands or who are already receiving immunosuppression for another reason.

References

1. Wilson FR. The hand: how its use shapes the brain. Language, and human culture. 1st ed. New York: Pantheon Books; 1998. Pp. xiv, 397.
2. Dunbar R. Grooming, gossip and the evolution of language. Cambridge (MA): Harvard University Press; 1996.
3. Donald M. Origins of the modern mind: three stages in the evolution of culture and cognition. Cambridge (MA): Harvard University Press; 1991.
4. Moore FD. Ethical problems special to surgery: surgical teaching, surgical innovation, and the surgeon in managed care. *Arch Surg* 2000; 135(1):14–16.
5. Dubernard JM, Owen E, Herzberg G, et al. Human hand allograft: report on first six months. *Lancet* 1999; 353:1315–1320.
6. Jones JW, Gruber SA, Barker JH, Breidenbach WC. Successful hand transplantation. One-year follow-up. Louisville Hand Transplant Team. *N Engl J Med* 2000; 343:468–473.
7. Siegler M. Ethical issues in innovative surgery: should we attempt a cadaveric hand transplantation in a human subject? *Transplant Proc* 1998; 30:2779–2782.
8. Malt RA, McKhann CF. Replantation of severed arms. *JAMA* 1964; 189:716–722.
9. Chen CW, Chien YC, Pao YS. Salvage of the forearm following complete traumatic amputation; report of a case. *Chin Med J* 1963; 82:632.

10. Zhong-Wei C, Meyer VE, Kleinert HE, Beasley RW. Present indications and contraindications for replantation as reflected by long-term functional results. *Orthop Clin North Am* 1981; 12(4):849–870.
11. Lee WP, Mathes DW. Hand transplantation: pertinent data and future outlook. *J Hand Surg [Am]* 1999; 24(5):906–913.
12. Meyer VE. Hand amputations proximal but close to the wrist joint: prime candidates for reattachment (long-term results). *J Hand Surg [Am]* 1985; 10(6 Pt 2):989-991.
13. Tamai S. Twenty years' experience of limb replantation — review of 293 upper extremity replants. *J Hand Surg [Am]* 1982; 7(6):549–556.
14. Tark KC, Kim YW, Lee YH, Lew JD. Replantation and revascularization of hands: clinical analysis and functional results of 261 cases. *J Hand Surg [Am]* 1989; 14(1):17–27.
15. Jones TR, Humphrey PA, Brennan DC. Transplantation of vascularized allogeneic skeletal muscle for scalp reconstruction in a renal transplant patient. *Transplant Proc* 1998; 30:2746–2753.
16. Guimberteau JC, Baudet J, Panconi B, et al. Human transplant of a digital flexion system vascularized on the ulnar pedicle: a preliminary report and 1-year follow-up of two cases. *Plast Reconstr Surg* 1992; 89:1137–1147.
17. Hofmann GO, Kirschner MH, Wagner FD, et al. Allogeneic vascularized transplantation of human femoral diaphyses and total knee joint: first clinical experiences. *Transplant Proc* 1998; 30:2754–2761.
18. Strome M, Stein J, Esclamado R, et al. Laryngeal transplantation and 40-month follow-up. *N Engl J Med* 2001; 344(22):1676–1679.
19. Lee WP, Yaremchuk MJ, Pan YC, et al. Relative antigenicity of components of a vascularized limb allograft. *Plast Reconstr Surg* 1991; 87(3):401–411.
20. Min Z, Jones NF. Limb transplantation in rats: immunosuppression with FK-506. *J Hand Surg [Am]* 1995; 20:77–87.
21. Fealy MJ, Umansly WS, Bickel KD, et al. Efficacy of rapamycin and FK-506 in prolonging rat hind limb allograft survival. *Ann Surg* 1994; 219:88–93.
22. Benhaim P, Anthony JP, Lin LY, et al. A long-term study of allogeneic rat hindlimb transplants immunosuppressed with RS-61443. *Transplantation* 1993; 56(4):911–917.
23. Benhaim P, Anthony JP, Ferreira L, et al. Use of combination of low-dose cyclosporine and RS-61443 in a model of composite tissue allotransplantation. *Transplantation* 1996; 61(4):527–532.
24. Lance EM, Inglis AE, Figarola F, Veith FJ. Transplantation of the canine hind limb. Surgical technique and methods of immunosuppression for allotransplantation. A preliminary report. *J Bone Joint Surg Am* 1971; 53:1137–1149.
25. Goldwyn RM, Beach PM, Feldman D, Wilson RE. Canine limb homotransplantation. *Plast Reconstr Surg* 1966; 37:184–195.
26. Daniel RK, Egerszegi EP, Samulack DD, et al. Tissue transplants in primates for upper extremity reconstruction: a preliminary report. *J Hand Surg [Am]* 1986; 11:1–8.
27. Stark GB, Swartz WN, Narayanan K, Moller AR. Hand transplantation in baboons. *Transplant Proc* 1987; 19:3968–3971.
28. Hovius SE, Stevens HP, van Nierop PW, et al. Allogenic transplantation of the radial side of the hand in the rhesus monkey: I. Technical aspects. *Plast Reconstr Surg* 1992; 89:700–709.
29. Stevens HP, Hovius SE, Heeney JL, et al. Immunologic aspects and complications of composite tissue allografting for upper extremity reconstruction: a study in the rhesus monkey. *Transplant Proc* 1991; 23(1 Pt 1):623–625.
30. Ustuner ET, Zdichavsky M, Ren X, et al. Long-term composite tissue allograft survival in a porcine model with cyclosporine/mycophenolate mofetil therapy. *Transplantation* 1998; 66:1581–1587.
31. Jones JW, Ustuner ET, Zdichavsky M, et al. Long-term survival of an extremity composite tissue allograft with FK506-mycophenolate mofetil therapy. *Surgery* 1999; 126:384–388.
32. Barker JH, Jones J, Breidenbach WC, editors. Proceedings of the international symposium on composite tissue allotransplantation. *Transplant Proc* 1998; 30:2687–2787.
33. Jones NF. Debate: concerns about human hand transplantation in the 21st century. *J Hand Surg* 2002; 27A:771–787.
34. Francois CG, Breidenbach WC, Maldonado C, et al. Hand transplantation: comparison and observation of the first four clinical cases. *Microsurgery* 2000; 20:360–371.
35. Carroll D. A quantitative test for upper extremity function. *J Chron Dis* 1965; 18:479–491.
36. Herndon JH. Composite-tissue transplantation — a new frontier [editorial]. *N Engl J Med* 2000; 343:503–505.

Uterus Transplantation

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Abstract

Until recently, only life and death situations warranted organ transplantation. Nonvital transplantation, to further a patient's wishes and goals, was not considered justified. It can be argued, however, that this distinction is not morally significant. Patients with kidney failure, for example, can be kept alive by dialysis. But their quality of life would be greatly enhanced by kidney transplant, which is thus considered a justified procedure. So a spectrum of rationales may justify transplantation. Transplantation of the uterus would relieve the anguish of women who greatly desire to conceive a child. Some women do not have a uterus. In some cases this is due to a congenital absence (Rokitansky's syndrome). In other cases, surgical removal of the uterus was required to repair an obstetrical rupture. With a transplanted uterus, many of these women could have the opportunity to become pregnant as a result of nonvital organ transplant.

While other organ transplant donations most often come from cadavers and less often from living donors (kidney or partial liver), the donor source for a uterus may be an otherwise healthy living patient who requires uterus removal as a standard care procedure. Furthermore, it should be possible to remove the transplanted uterus from the recipient after successful pregnancies, so the patient would not be subjected to lifelong antirejection medications.

Since animal uterus transplantation has been done successfully, human uterus transplantation might be considered for select cases. One such case has been reported.

Key Words: Uterus transplantation, quality of life surgery, prolapse uterus utilization, ethics.

Introduction

PEOPLE UNFAMILIAR WITH TRANSPLANTATION tend to think of it as only a life-saving procedure. This picture of transplantation, however, is not consistent with the longstanding facts. For more than twenty-five years, kidney transplantation has significantly improved patients' quality of life, even though dialysis is a life-preserving alternative. In addition, corneal transplant is a well-accepted therapy, and it is performed only to improve a patient's quality of life, not to preserve it. For similar reasons, autotransplantation, such as reattaching severed limbs, has been recognized as an ethical procedure. In what follows, the possibility of uterine transplant will be assessed as an intervention that will significantly improve a patient's quality of life.

In the past, skepticism about nonvital transplantation procedures was justified by the high likelihood of organ rejection. But, over the past two decades, transplantation technology and immunosuppression have advanced and the prognosis of transplantation has improved. These advances make transplantation a possible new treatment option for patients who wish to improve their quality of life.

Questions Pertaining to Uterus Transplantation

The Ethics Committee of the American Society for Reproductive Medicine has never addressed the issue of uterine transplantation. Its reports have focused on the ethics of procedures that are already being performed, not on possible future procedures. Before the procedure is performed, we must consider two crucial questions. Is uterine transplantation feasible? Is it justified?

The uterus enables a woman to menstruate and become pregnant. Most would agree that merely being able to menstruate is not important enough to justify the risks associated with solid organ transplantation. But for many

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women, the ability to become pregnant can be very important. For them, childbearing fills a deep emotional and social need, and they may feel a corresponding sense of loss if they are unable to conceive and give birth.

It is likely that for many women the intense desire to become pregnant is, at least in part, an innate feature of evolutionary biology. But there may be a stronger social component to this desire. Historically, in many cultures, to be barren was to be cursed. Having a child, on the other hand, meant that one was blessed and honored, perpetuating a family and a name. Yet desire alone does not justify transplantation. This emotional need has to be balanced against the feasibility of transplantation and the possible risks to the woman and child.

A uterine transplant could be an appropriate treatment for women who have no uterus but whose reproductive system is otherwise normal. For some women, the absence of the uterus is a congenital problem (known as Rokitansky's syndrome, or Müllerian agenesis). Other women may not have their uterus because of a previous hysterectomy, or they may be at risk for a uterine rupture should they become pregnant (Table).

Women who have had a hysterectomy or who have a high risk of rupture, and have already been pregnant, have the advantage of having large uterine vessels, which might facilitate the vascular anastomoses of a uterine transplant and increase the chance of a vaginal delivery.

A variety of considerations will make a woman a good candidate for uterine transplantation:

- an intense desire to become pregnant
- a good understanding of the known and an

appreciation of the unknown risks associated with the transplant and with postoperative long-term immunosuppression

- emotional maturity
- ability to give informed consent
- excellent general health
- age under 35 — older patients have a lower chance of achieving pregnancy and a greater chance of having complications (e.g., hypertension, diabetes and uterine fibroids) and needing cesarean section.
- no evidence of inability to be a good mother
- expectation that the patient will comply with regimens of post-transplant immunosuppression and monitoring

Rokitansky's Syndrome Patients

Patients with the Mayer-Rokitansky-Küster-Hauser syndrome, or Müllerian agenesis, have congenital absence of the uterus and vagina. Their ovaries, however, are present, with normal function and ovulation. The fallopian tubes may or may not be present. About one-third of these patients also lack a kidney but have normal renal function and normal chromosomes. These patients also have normal female physical characteristics and behavior.

This syndrome is usually diagnosed between ages 15 and 17, when the patient seeks medical treatment for amenorrhea (i.e., the absence of menstruation). Theoretically, the condition should be diagnosed at birth or at well-child routine examinations. Unfortunately, many pediatricians were never trained to inspect the vulva or may avoid performing the examination due to fear of accusations of lewdness. In addition, when the question of amenorrhea is raised, pediatricians often give incorrect reassurance that the patient is maturing normally, due to evidence of increased height, breast development, the appearance of pubic and axillary hair, feminine contour, and psychological development. Furthermore, tests of hormones, ovulation and chromosomes would all provide normal results.

In my consultation practice, I am sometimes the first to examine the patient for abnormalities. Although the vulva looks normal, there is only a dimple where the opening of the vagina should be (Fig. 1). On rectal examination, the cervix and uterus cannot be palpated. These findings are sufficient for the presumptive diagnosis. The patient will never menstruate and she

TABLE

Women Who Need a Uterus to Become Pregnant

1.	Congenital anomalies
a)	Rokitansky syndrome (Müllerian agenesis): congenital absence of uterus and vagina
b)	rudimentary noncommunicating or nonfunctioning uterine horn
2.	Previous hysterectomy for
a)	postpartum hemorrhage
b)	invasive adherent placenta accreta
c)	rupture of uterus during pregnancy
1)	difficult delivery
2)	rupture of scar of previous caesarean section
3.	High risk of rupture of uterus
a)	previous pregnancy rupture and repair of classical caesarean section scar
b)	previous very extensive myomectomies or removal of extensive adenomyosis