Background

Transplantation conceptually dates back to archeologic records from thousands of years ago with dramatic advancement over the past sixty years (1). Early attempts at solid organ transplantation were met with graft rejection, as knowledge of immunology was still rudimentary. In 1936, Russian surgeon Yuriy Voronoy performed a renal transplant with ABO incompatibility, which failed to produce urine and the recipient died two days later (1). From 1951–1952, David Hume and colleagues at Brigham Hospital in Boston performed nine renal transplants, with each resulting in allograft rejection (1). In 1954, Murray and Merrill performed the tenth renal transplant at Brigham Hospital from an identical twin donor, and the graft remained functional until recurrent glomerulonephritis nine years later (2,3). Initial immunosuppression was attempted with whole body radiation, which led to severe side effects resulting in death after transplantation (4). In the late 50’s, pharmacologic advances lead to the evaluation of 6-mercaptopurine in animal studies (5). However, even at decreasing doses the drug was found to be toxic in human transplant patients (6). A breakthrough for solid organ transplantation in the 1960’s was the development of azathioprine. When used in combination with corticosteroids for solid organ transplantation, it facilitated host tolerance and decreased rejection (7).

Soon after kidney transplantation, liver transplantation was developed and was met with technical challenges. One year survival was poor, similar to renal patients, due to the immunocompromised state (8). Initial cardiac, pancreatic, and pulmonary transplantations occurred in the late 1960’s with poor long-term success (9). Further discovery of immunomodulation, with development of the calcineurin inhibitors, lead to improved graft and patient survival from the mid-1980’s through present day (9). Additionally, this period correlated with the discovery and further understanding of the role of major histocompatibility complex (MHC) and human leukocyte antigens (HLA) in transplantation (10).

Successful efforts in solid organ transplantation spawned interest in composite tissue allotransplantation (CTA). The United Network for Organ Sharing (UNOS) defines a CTA as having the following criteria: (I) vascularized and...
Penile replantation was first reported in 1929 by Ehrich et al., featuring a macroscopic technique in which no neurovascular anastomoses were performed (19). This macroscopic technique led to poor results with eventual skin loss. Their approach included anastomosis of the urethral mucosa, corpora spongiosum, and tunica albuginea of both corpora cavernosa in a watertight fashion. Microscopic penile replantation was first reported in 1976 with improved outcomes (20). In 2004, Landstrom et al. reviewed the cases of complete penile transection and replantation (21). The review included 28 cases with 16 suffering complications, of which 14 had preputial loss. The number of penile arteries and veins required for perfusion is controversial, with the review supporting the need for repair of at least one dorsal artery. One case omitted dorsal arterial anastomosis, and despite anastomosis of two profundus arteries, the operation resulted in necrosis of the glans and foreskin (20). Anastomosis of the arteries should be performed first to allow for reduction in ischemia time. The role of cavernosal artery anastomosis is controversial. In the Landstrom et al. review, 3 of 6 patients had erections with cavernosal artery anastomoses compared to 15 of 22 without cavernosal artery approximation (21). Some argue that the vascular flow provided by the cavernosal arteries is low and prolonged operative time to perform this maneuver can lead to further damage to erectile tissue. Venous outflow is essential for limiting postoperative edema and to promote preservation of skin with some advocating maximizing the number of attainable superficial and deep venous anastomoses (22). Anastomosis of the dorsal nerve is performed subsequent to reestablishing vascular flow. Perioperative management of replantation includes antibiotic coverage, anticoagulation, use of hyperbaric oxygen, penile immobilization, and wound care.

Penile transplantation

Penile transplantation has been demonstrated in animal models. In one study, penises from Brown-Norway rats were removed and placed in an omental pouch of Lewis rats immunosuppressed with FK506 (tacrolimus), with absence of rejection on pathology (23). Another study involved penile transplantation between Beagles with microvascular anastomoses of neurovascular structures (24). The dogs were maintained on a regimen of FK506, mycophenolate mofetil (MMF), corticosteroids, and antibiotics. Catheters were removed on day 7 with voids recorded. On day 14, the transplanted penises were resected for pathologic review. Among 20 transplants, venous and arterial anastomoses...
were successful in 95% and 87.5%, respectively. Significant swelling was noted in every case, with three cases experiencing glans necrosis. Urination was normal in all subjects, and cystourethrography on day 10 confirmed universal absence of stricture. Pathology confirmed patent vasculature, limited infiltration of inflammatory cells, and absence of interstitial necrosis.

Guangzhou General Hospital in China reported the first human penile transplantation in 2006 (25). The recipient was a 42-year-old male with a history of traumatic penile amputation eight months prior, and the organ was from a 22-year-old brain-dead donor. The parents of the donor provided consent, the donor and recipient were crossmatched for HLA, panel reactive antibodies and blood type, and approval was obtained from the hospital’s ethical committee. The urethral mucosa was re-approximated, followed by corpora spongiosum, and the tunica albuginea of both corpora cavernosa. The deep dorsal vein, dorsal artery, and dorsal nerve were then reconstituted, followed by the superficial dorsal vein after closure of Buck’s fascia. Induction included daclizumab, MMF, and methylprednisolone. The maintenance regimen consisted of MMF, prednisone, and cyclosporine. Venous stasis and edema resulted in loss of the distal penile skin. The urethral catheter was removed on postoperative day 10. On postoperative day 14, the patient and his wife requested graft removal due to psychological concerns based on aesthetic appearance. Pathology confirmed absence of rejection.

This initial report prompted ethical concerns. The treating hospital subsequently released 10 principles for penile transplantation after case review (26). These included defining the target population, as well as the need to establish protocols and a review board for each case inclusive of a multidisciplinary team of surgeons, transplant specialists, pharmacists, and psychological support for recipient and partner. Thorough preoperative evaluation and informed consent for donor and recipient were also deemed essential.

The next incidence of human penile transplantation was performed in December 2014 at Tygerberg Hospital in South Africa. The patient was a 21-year-old male with penile loss due to complications from ritual circumcision. This problem afflicts approximately 250 South African men annually resulting in psychological distress and even contemplation of suicide (27). The 9 hour operation was led by Dr. Andre van der Merwe. This was reportedly challenging due to extensive fibrosis and disruption of native vasculature. The dorsal nerve was successfully reconstituted. The dorsal artery of the graft was fed by the recipient’s inferior epigastric and superficial external pudendal arteries (27). Postoperatively, additional procedures were required secondary to thrombosis of the penile artery, an infected hematoma, and development of urethral fistula. It has been reported that the recipient had psychological improvement, intact skin sensation, and erectile function (28). It was also stated that natural conception was achieved, although this resulted in stillbirth (28).

In May 2016, surgeons at Massachusetts General Hospital in Boston reported success with penile transplantation in a 64-year-old patient who previously underwent penectomy for penile cancer (28). Reports state the recipient had been cancer free for several years. The procedure took 15 hours and involved the participation of 13 surgeons (28). An episode of rejection was treated without complication (28). Sexual function is yet to be determined, but normal voiding was confirmed upon removal of catheter 3 months postoperatively (28).

**Perioperative management**

Perioperative management of penile transplantation requires a multidisciplinary approach. Donors should be screened for EBV, CMV, hepatitis B and C, and HIV serology (29). Additionally, close examination for penile lesions is necessary in an immunocompromised recipient. ABO and HLA compatibility should be assessed to prevent rejection. It is unclear if immunosuppression will need to be lifelong. Rates of rejection for CTA exceed that of solid organ transplantation due to the antigenic contribution of skin. Acute rejection of CTA has been reported in an excess of 85% (30). Immunosuppression for CTA mirrors that of solid organ transplants. Induction involves antithymoglobulin, daclizumab, basiliximab, alemtuzumab, or high dose steroids. Maintenance immunosuppression is typically a combination of MMF, prednisone, and FK506.

Postoperative wound care involves attention to edema and signs of impending skin loss. Biopsy may be required to determine need for adjusting immunosuppression. Chronic rejection of CTA is also a concern. This process targets the skin and deep vessels, potentially resulting in dermal sclerosis and graft loss (31). In patients who regain potency, monitoring of erectile function may allow detection of chronic rejection secondary to corporal fibrosis.

Subsequent clinical evaluations should also assess voiding...
Ethical considerations

Penile transplantation includes medical, cultural, emotional, and even religious concerns. As with other CTA, penile transplantation is a quality-of-life, rather than a life-saving procedure. Medical considerations involve the screening and immunosuppression previously described. Immunosuppression in patients with a history of penile cancer raises concerns, and optimal cancer free interval may need to be determined. Most transplantation protocols require recipients to be free of solid organ and skin cancer for 2–5 years prior to listing (33). Immunosuppression increases the risk of bacterial and viral infections, as well as that of secondary malignancies. In light of this, considering a quality-of-life procedure that may threaten patient longevity, a detailed risk benefit analysis is essential. Additionally, the threshold to remove the transplanted organ should be discussed preoperatively.

Emotional concerns involve not only the recipient and his potential partner(s), but also the parties involved in consideration of organ donation. Some families view donation for CTA as mutilation, and there may be a social stigma associated with the donation of genitalia of a family member. Studies involving CTA have shown that the general public is unaware that the face and hands can be donated, and the question will also need to be posed as it relates to genitalia (34). A New Jersey study of 1,000 individuals noted a greater willingness to donate solid organs over either hand or face (35). Awareness and public education regarding donation for CTA is critical.

Detailed psychosocial assessment of potential recipients and their respective partners appears to be essential. The outcome of the case in China demonstrates the need for proper counseling and informed consent (26). There is also a need for privacy despite the interest by the media. Patients are likely to require social support and should be assessed for the ability to cope with the possible stigma and even publicity. It is understandable how this may be especially challenging with receipt of a sexual organ as opposed to a solid intraabdominal organ.

Religion and culture play an especially interesting role in penile transplantation for donors and recipients. The question of sexual sin is unique to this form of transplantation, and some may view such sin as being passed with the genitalia. Christianity asserts the role of caring for the sick and dying, lending itself to the support of organ donation. However, in 2009, Pope Benedict XVI wrote an open letter that included the prohibition of transplantation of gonads and organs connected to personal and procreative identity (36). Muslim scholars differ on the Islamic definition of brain-death (37). However, the Islamic position is that organs responsible for fertilization and satisfying sexual desire should not transferred from one human to another (38). Conservative and Reformist Judaism encourage organ donation, and there is no clear consensus of brain-death among orthodox leaders (39). Organ donation has been part of Hindu myths and writings without clear discussion related to genitalia (40). Buddhism and confucian ethics debate the time of death and the role of a lingering spirit afterwards, making the concept of donation somewhat complicated (41,42).

Future considerations

Further application of penile transplantation raises the possibility of considering more controversial patient populations, such as those with congenital micropenis or those considering sexual reassignment. This raises additional ethical questions as well as technical postulation of feasibility in transplanting a male phallus to a female recipient. Additionally, patients that have suffered traumatic blast injuries, as seen in wounded members of the military, may present a formidable challenge due to significant disruption of the neurovascular anatomy within the pelvis.

As we move forward within an era full of promise, patience is a virtue of the utmost importance. Failures will be encountered but should not deter investigation of
what is likely to be an operation which provides dramatic improvement in quality of life among properly selected individuals. Had the first nine failures prevented Murray and Merrill from performing their first successful renal transplant, the world would be a vastly different place.

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Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.

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