Chapter 2  
Vascularized Composite Allotransplantation

Abstract In order to discuss the ethics of vascularized composite allotransplantation (VCA), it is necessary to have a firm grasp of this rapidly developing field, including its history, its present state and its anticipated future directions. The story of the development of VCA began in the imaginations of ancient peoples, but required important medical and surgical advances for the practice to become a reality. A survey of the history of VCA will emphasize the role of advances in surgical techniques, including anastomosis of blood vessels and nerves and the emergence of microsurgery. It will also review the emergence of a better understanding of immunology and the development of effective means of immunosuppression. A brief survey of the beginnings of solid organ transplantation and limb replantation will be offered, as they together formed the technical foundation for the first attempts at VCA. The current state of VCA, with a special focus on facial and upper extremity transplantation, will be explored, as will be issues of practical and ethical concern.

2.1 Introduction

Vascularized composite allotransplantation (VCA) holds out great promise as a treatment for devastating facial and upper extremity defects. However, it also demands a great deal from patients in terms of both foreseeable burdens and possible risks. In light of the fact that these burdens and risks are undertaken in the course of treatment which is not necessary to preserve or extend life, because VCA candidates may be regarded as especially vulnerable, and given that long term graft survival remains uncertain, serious ethical questions have been generated. Indeed, the ethical justification of VCA has been developing simultaneously with the practice itself. As part of the effort to provide ethical justification for facial and upper extremity VCA, this book proposes “covenant consent,” a more robust form

\[1\] Kiwanuka et al., 1558–1568; Chang and Mathes, 553–560.

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of consent which addresses some of the special conditions associated with VCA. In order to explain why covenant consent is especially fitting for VCA, it is first necessary to give a thorough description of VCA, including its development and its antecedents in solid organ transplantation (SOT) and limb replantation. Such a thorough description, including descriptions of ethical issues that have been raised concerning VCA, will be the focus of this chapter.

2.2 History and Development of Solid Organ Transplantation and Limb Replantation

Since 1988, more than a half million organ transplants have taken place in the United States alone, with recipients aged less than a year to over 80 years. The scale of SOT is all the more remarkable given that the earliest verifiably successful organ transplantations occurred little more than half a century ago. Yet, while SOT only became a well-established clinical practice in the last fifty years, there is ample evidence that the possibility of transplanting organs and tissues fired the imaginations of ancient peoples and the first experimental efforts in the modern age took place long before the surgical techniques and understanding of immunology necessary for success were available.

2.2.1 Ancient Evidence

According to historians of medicine, some of the earliest descriptions of transplantation come from Hindu literature, in which descriptions are found of skin transferred from a patient’s buttocks to repair defects of the face. Accounts of the transfer are found in the Sushutra Samhita Sanskrit texts and dated to the third millenia B.C.E. This method of autologous transplantation is essentially the same approach that is used in modern medical practice to treat most major facial defects due to traumatic injury. Other forms of transplantation which appear credible are also mentioned in ancient sources, including transplantation of teeth and bone. There are reports from ancient Egypt of slaves being forced to donate teeth to

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3Credit for the first “successful” organ transplant is usually given to a team headed by Joseph E. Murray at the Peter Bent Brigham Hospital of Boston in 1954. See, for example, Ortega, 17.

4Howard, Cornell and Cochran, 6; Linden, 165–166.

pharaohs who desired them for replacing their own. Other attempts at the transplantation of teeth took place in ancient Greece and Rome, and continued until the late 18th century when physicians became concerned that the transplants played a role in the transmission of contagious diseases, including syphilis. Bone grafts are also reported. In addition to these literary descriptions of relevant types of surgery, archeological evidence exists for trephination, the temporary removal and later replacement of skull bone to treat brain swelling. Less credible or more likely mythological descriptions of transplantation found in ancient sources include a double heart transplant by Chinese physician Pien Chi’ao and the transplantation of a leg by legendary Christian physicians, St. Cosmas and St. Damian.

2.2.2 Developments in Transplantation Prior to 1954

In the 19th century, experimentation with transplantation began to flourish. According to Alexis Bergan, human grafts attempted during that century included “skin, tendons, nerves, cartilage, adipose, corneas, adrenal and thyroid glands, ovaries, partial digestive and urinary tracts, and muscle.” Swiss surgeon Theodor Kocher attempted a thyroid transplant as early as 1883. Extensive experimentation with animals took place during the same period and into the first half of the 20th century, including some work on xenotransplantation. Alexis Carrel, whose development of vascular anastomic suturing was critical to the development of transplantation, experimented with cats and performed a heart transplant in a dog. Others worked with rabbits, pigs and macaques. French physician Mathieu Jaboulay tried to implant kidneys from pigs and goats into humans.

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7Cohen, Shen and Pogrel, 481.
8Linden, 166.
12Bergan, 3. See also Howard, Cornell and Cochran, 7, for a similar list dated to 1923.
14Howard, Cornell and Cochran, 7; Linden, 166.; Schlich, 1373.
15Linden, 167.
16Schlich, 1373.
Among the more unusual early experiments with xenotransplantation were some which took place in the fourth decade of the 20th century. Notable among these were an attempt to transplant a uterus into a transgender woman in Denmark in 1931, and the efforts of the Russian Dr. Serge Voronoff to address loss of libido. Voronoff, after finding younger men reluctant to donate, attempted to treat reduced libido by transplanting monkey testicles into older men. Voronoff was likely inspired in part by the reports of physicians in the United States who had claimed success in human-to-human testicular transplants. Sources of such reports included Dr. Frank Lydston of Chicago, who claimed to have performed the surgery on himself as well as others, and Dr. L.L. Stanley of San Quentin prison, who reported transplanting the testicles of a deceased prisoner into a living prisoner in an attempt to reverse premature senility.

Ortega describes this era of transplantation history as a “muddled period,” and many of the experiments do seem absurd in retrospect. Even so, important advances in technique were taking place. Chief among them was the achievement of Alexis Carrel in developing methods for successfully attaching donor and recipient blood vessels. His skill in doing so enabled him to succeed in autologous transplants, and this success paired with failure while using the same techniques in allotransplantation precipitated investigation into the dynamics of rejection.

A second technical advancement relevant to transplantation took place during this same period, though it would not be applied to transplant surgery until much later. In 1921, Swedish otolaryngologist Carl Olof Nylen pioneered microsurgery. Nylen, a young assistant in the ENT department in Stockholm used a monoscope to repair the inner ear. Two and a half decades later, microsurgical techniques were first used in ophthalmic surgery, when Chicago ophthalmic surgeon Richard A. Perritt employed a binocular microscope. The use of microsurgery for the treatment of cataracts quickly became a standard procedure. Soon thereafter experiments in vascular microsurgery involving animals began. Only in 1960, however, did microsurgery first begin to be employed on humans for the purpose of vascular

\[\text{\textsuperscript{18}}\text{Howard, Cornell and Cochran, 7.}\]
\[\text{\textsuperscript{20}}\text{Ortega, 14.}\]
\[\text{\textsuperscript{21}}\text{Schlich, 1373; Linden, 166–167.}\]
\[\text{\textsuperscript{23}}\text{Tsu-Min Tsai, Juan M. Breyer, and Joao B. Pannatoni, “History of Microsurgeries: Curiosities from the Sixties and Seventies,” Microsurgery 33, no. 2 (2013): 85.}\]
repair, anastomosis and nerve repair, all of which would prove critical to the success of limb replantation and VCA.\textsuperscript{24}

The absence of an effective method of addressing transplant rejection cooled the ardor of researchers as the 20th century moved into its fourth and fifth decades. Only a few transplants were attempted during this period, primarily involving kidneys for patients very near death. In 1933 Yury Voronoy of Russia transplanted a kidney into a young woman who had suffered mercury poisoning. Sources differ on whether the kidney functioned poorly or not at all, but agree that the woman died two days post-transplant.\textsuperscript{25} A certain degree of success was achieved with what may be characterized as a “bridge” transplant in 1947. A Boston surgeon placed a donor kidney into a woman whose own kidneys had stopped working due to a uterine infection. The donor kidney functioned for a few days, until the recipient’s infection subsided and her own kidneys began to function again.\textsuperscript{26} In 1952, French surgeons transplanted a kidney from a living donor into the donor’s son and that kidney functioned for three weeks before overwhelming rejection occurred.\textsuperscript{27}

During the Second World War, research biologist Peter Medawar was called upon by the Medical Research Council of Great Britain to carry out studies to determine why skin grafts from donors consistently failed to survive when transplanted. Medawar took up experimentation on animals, and developed theories of immune response which ultimately led to his receiving the Nobel Prize.\textsuperscript{28} Based on Medawar’s work demonstrating that rejection was a reaction of the immune system, early efforts to suppress the immune system were attempted. These included sub-lethal whole body radiation and the use of prednisone.\textsuperscript{29} Unfortunately, rejection soon took place in every case.\textsuperscript{30}

\subsection*{2.2.3 Early Developments in Replantation}

Replantation of digits, limbs and other body parts has its own history, though many of the same techniques that would become essential for allotransplantation of solid

\begin{itemize}
\item \textsuperscript{25}Ortega, 14; Howard, Cornell and Cochran, 7; Linden, 167; Bergan, 4.
\item \textsuperscript{26}Bergan, 4; Howard, Cornell and Cochran, 7.
\item \textsuperscript{27}Ortega, 17.
\item \textsuperscript{28}Peter Medawar Biographical, accessed January 7, 2015. \url{http://www.nobelprize.org/nobel_prizes/medicine/laureates/1960/medawar-bio.html}.
\item \textsuperscript{30}Linden, 167; Howard, Cornell and Cochran, 7.
\end{itemize}
organs would also be critical in the development of more complex replantations. There is evidence for attempts at replantation during the Middle Ages, as one medical author of the period insists that it is not possible to replant body parts which have been amputated. Successful nose replantation is reported in the 16th century, and beginning in the 19th century there are reliable reports of digit replantation. Alexis Carrel, who established the technique of vascular anastomosis, employed it in the replantation of canine limbs, as did William Stewart Halstead, in the early 20th century.

Replantation is not subject to immunological rejection, and given the success in animal models early on, it is somewhat surprising that the earliest successful vascularized limb replantation did not take place until some years after the earliest successful allotransplantation of an organ, though earlier attempts at limb replantation were made.

2.2.4 Sixty Years of Successful Solid Organ Transplantation

The first solid organ transplantation with long-term graft survival took place in 1954 at Peter Bent Brigham Hospital. Surgeons Joseph Murray and John Merrill successfully transplanted a kidney from the recipient’s identical twin. The recipient survived for eight years post-transplant. While certainly noteworthy, this success did not signal the beginning of large scale transplantation of organs, as it did not involve finding a solution to the immunological barriers. Not long afterward, however, the use of a combination of azathioprine and prednisone opened the door to successful solid organ transplantation on a large scale.

Kidney dialysis expanded the pool of potential transplant candidates, and indirectly led to the development of a system of procurement and allocation. Within twenty years of Murray and Merrill’s successful kidney transplant, several other organs came to be transplanted successfully, including livers, hearts, and lungs. While graft and recipient survival increased substantially as experience was gained, problems persisted. In particular, the side effects of the immunosuppressant regimens compromised quality of life and sometimes proved fatal. Advancements

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31Kocher, 462.
32Kocher, 462–463.
33Kocher, 464.
34Kocher, 465; Tamai, 283e.
35Bergan, 5; Howard, Cornell and Cochran, 7; Linden, 167.
37Linden, 168.
38Linden, 169–170; Bergan, 8.
in immunosuppression, including the development of cyclosporine in the 1970s, tacrolimus in the 1980s, and mycophenolate mofetil in the 1990s, ameliorated but did not eliminate toxic side effects. Problems with the side effects of immunosuppression have spurred renewed interest and substantial research into immunomodulation and induced tolerance.

2.2.5 Developments in Replantation

Roughly concurrent with the development of successful solid organ transplantation has been the emergence of established replantation programs. In 1962, Ronald A. Malt, then chief surgical resident at Massachusetts General Hospital, replanted the arm of a twelve-year old boy after the boy had suffered above the elbow amputation. From that point forward, efforts to replant upper extremities increased, with progress in technique coming from Japan and China as well as from the United States and Europe. Microsurgery played a key role, permitting the anastomosis of very small blood vessels and the repair of nerves, leading to much improved function. Of course, optimal restoration of function also depended on the development and application of appropriate physiotherapy following surgery. Limb and digit replantation has become a well-established practice, with thousands of procedures taking place since Malt’s pioneering efforts. Replantation for vascularized tissues other than upper extremities increased as the decades passed. This included work on flaps containing skin, muscle and adipose tissue, preparing the way for face transplantation as well as upper extremity transplantation.

2.3 History and Development of Vascularized Composite Allotransplantation

Vascularized composite allotransplantation (VCA) is the name now used for transplantation of anatomical structures composed of multiple tissue types. The term “reconstructive transplantation” is also used, and until recently, the term

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39 Linden, 169–170; Sayegh and Carpenter, 2762; Bergan, 6; Ortega, 22–24.
41 Kocher, 465; Tamai, 283e; Alexandros Beris et al., “Digit and Hand Replantation,” Archives of Orthopaedic and Trauma Surgery, 130, no. 9 (2010): 1141; Tsai, Breyer and Panattoni, 85.
42 Tamai, 285e–287e.
44 Tamai, 290e–291e.
composite tissue allotransplantation was more common. The term, “Composite tissue transplantation,” was first employed by Earle Peacock, Jr., in 1957 to describe his attempts to transplant flexor tendons. Part of the rationale behind the change in nomenclature from composite tissue allotransplantation to vascularized composite allotransplantation was to avoid confusion as the system of procurement under U.S. law treats tissues very differently than it does organs. A similar shift in nomenclature and regulation has taken place in Europe, with VCAs being originally excluded from consideration as organs, but included as of 2012.

VCA may also be understood as a sub-type of CTA, which includes both vascularized and non-vascularized tissues. Examples of the latter would include transplantations of tendons, subcutaneous fat and some bones. Much of the focus of VCA thus far has been on upper extremity and facial VCA, though other forms have also been attempted.

Experience with solid organ transplantation and replantation led to the development of the necessary surgical and rehabilitative skills for successful VCA many years ago, but the high rate of immunogenicity of skin dampened enthusiasm for VCA procedures until more advanced immunosuppressants became available. In 1996, the use of cyclosporine and mycophenolate mofetil was demonstrated to sustain a vascularized composite allotransplantation of a rat hind limb, and interest in the possibility of human VCA was rekindled.

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45Foroohar et al., 406.
48P. Petruzzo et al., “Long-term Follow-Up in Composite Tissue Allotransplantation,” 808; Shores, Imbriglia and Lee, 1863; Murphy, Zuker and Borschel, 2.
49Evans, “A Historical, Clinical, and Ethical Overview of the Emerging Science of Facial Transplantation,” 151; Diaz-Siso et al., 330.
Since the development of better immunosuppression, programs have proliferated, being established in several centers with sufficient resources to create the multidisciplinary teams required. Linda A. Evans describes the typical VCA team as being composed of surgeons, nephrologists, pathologists, immunologists, anesthesiologists, nurses, transplant coordinators, social workers, psychiatrists, dieticians, physical therapists and others. The total number of upper extremity and facial transplants attempted through early 2016 has surpassed one hundred.

### 2.3.1 Upper Extremity Transplantation

Upper extremity transplantation aims to provide significantly superior cosmetic and functional outcomes than are available through current prosthetic technology. Upper extremity amputation is much more likely to be experienced by young, otherwise healthy individuals than is lower extremity amputation, which is often the result of complications of diabetes in the elderly. By contrast, upper extremity amputation often occurs following a major sudden trauma to the limb, with the most common causes of injury being vehicle, farm and industrial accidents, blast injuries, electrical injuries and sepsis. Upper extremity amputation takes place at a number of levels, from wrist to shoulder disarticulation. Transradial amputation is the most common, and perhaps the most suited to later transplantation.

One estimate of the scale of upper extremity loss suggests that more than a half million people currently contend with some degree of upper extremity loss in the United States alone. Upper extremity transplantation is an option for persons who have defects, either congenital or due to injury, and who are dissatisfied with

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52Linda A. Evans, *The Experience of Health Care Team Members Involved in Facial Transplant Surgery and Patient Care: A Dissertation*, University of Massachusetts Medical School Graduate School of Nursing 2012: 13; 17–18.
mechanical prostheses. The transplant operation itself is basically the same as a replantation. Once the bone is fixed, tendons, arteries, nerves and veins are connected.

The possibility of upper extremity transplantation intrigued surgeons during the Second World War, leading to extensive planning but no actual attempt. The first attempted human limb transplant in the modern era took place in Ecuador in 1964, just as early solid organ transplantation was beginning to flourish. A single hand was transplanted to a bilateral amputee. Unfortunately, anti-rejection measures were not yet adequate, and the graft was lost within weeks. Interest in limb transplantation waned thereafter, based on the belief that the immunogenic load was too great, only to wax again as new immunosuppressants were developed in the 1980s. Foroohar et al., describe how a series of experiments with rat hind limb transplantation demonstrated the effectiveness of a combination including tacrolimus, mycophenolate mofetil, and cyclosporine in managing rejection, and how this spurred new enthusiasm toward the viability of VCA in humans.

After substantial animal research and amidst ethical debate, a French team performed a limb transplant in 1998. Jean-Michael Dubernard led the team which transplanted the right forearm of a brain dead donor to a 48 year-old male in a 13 h surgery. Considered a success at first, the graft was later lost due to the decision of the recipient to discontinue anti-rejection medications. Psychological issues were a major factor in this failure.

Just four months after the surgery in France, an American team in Louisville, Kentucky, performed a transplant to replace a left hand on 37 year old male, who retains the graft at the time of this writing. Other upper extremity transplants have followed elsewhere in the United States, as well as in Austria, China, Belgium, Italy, Great Britain, Spain, Poland, Turkey, Taiwan, Australia, Malaysia, Mexico.

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57 S. Salminger et al., report the rejection rate of all prostheses has been approximately 20% over the last quarter of a century. See “Hand Transplantation Versus Hand Prosthetics: Pros and Cons,” Current Surgical Reports 4, no. 8 (2016), epub.
58 Shores, Imbriglia and Lee, 1863.
61 Amer et al., 40; Errico, Metcalfe and Platt; Tintle et al., “Hand Transplantation,” 2; Ravindra et al., “Composite Tissue Transplantation,” 1238; Diaz-Siso et al., 330.
62 Ravindra et al., 1238.
63 Foroohar et al., 406.
64 M. Siegler, 2779–2782.
65 Ravindra et al., 1239; Amer et al., 40; Tintle et al., “Hand Transplantation,” 2; Errico, Metcalfe and Platt; Foroohar et al., 406.
and Iran. In January 2014, Tintle et al., reported eighty-nine upper extremity transplants had been performed worldwide. By November 2014, Shores, Brandacher and Lee reported 107 known transplanted hand/upper extremities on 72 patients worldwide.

Both single and double (bilateral) transplants of upper extremities have taken place, with the International Hand Registry established to track upper extremity transplantation showing nearly equal numbers of both types. The extent of transplant has also varied in terms of more distal and more proximal attachment sites. In general, the greatest return of function has taken place in the more distal grafts. The International Hand Registry (now the International Registry on Hand and Composite Tissue Transplantation) was founded in 2002 to collect information for the sake of supporting the practice and advancement of VCA. As of early 2014, 19 centers throughout the world had registered with the IRHCTT.

Upper extremity transplantation has also been combined with facial transplantation. The first face-and-hand recipient died sixty-five days after transplant, and the second recipient’s upper extremity grafts were removed due to necrosis five days after the initial surgery. Two additional deaths of upper extremity recipients have been reported from Turkey, but these cases included concomitant lower extremity transplants as well. Results for upper extremity transplants only have been very good when patients adhere to the immunosuppressive regimen, with reports of high levels of patient satisfaction. Still, successful upper extremity transplantation report that 100% of grafts have survived at least 1 year when the conventional triple-drug immunosuppression has been used.


Shores, Brandacher and Lee.

Pomahac, Gobble and Schneeberger, 1.

MacKay, Nacke and Posner, 77.

Gordon et al., 309–314; Petruzzo and Dubernard, 249; Siemionow, Gharb and Rampazzo, 638.

Foroohar et al., 408; Tintle et al.; “Hand Transplantation,” 5.

Shores, Brandacher and Lee, “Worldwide Update.” Tintle et al., “Hand Transplantation,” 4, report that 100% of grafts have survived at least 1 year when the conventional triple-drug immunosuppression has been used.

Shores, Imbriglia and Lee, 1862–1864; Ninkovic et al., 457–460; Foroohar et al., 406–409; Jensen et al., 2126–2135; Diaz-Siso et al., 331; Petruzzo and Dubernard, “World Experience,” 416. However, there have been reports of less-than-satisfactory outcomes that did not result in graft loss or patient mortality. See Singh et al., “Functional Outcomes after Bilateral Hand Transplantation: A 3.5 Year Comprehensive Follow-Up,” Plastic and Reconstructive Surgery 137, no. 1 (2016): 185–189. Jowsey-Gregoire et al., note that function does not always correlate with satisfaction.
involves significant burdens and carries substantial risks, while yielding results that fall short of full restoration of function.\textsuperscript{77} In light of these limitations, it is not surprising that attitudes among hand surgeons toward the procedure have remained mixed, with many skeptical of the practice.\textsuperscript{78}

### 2.3.2 Face Transplantation

Encouraged by the early successes in limb transplantation and experience with facial replantation following traumatic injury,\textsuperscript{79} surgeons and medical teams began to plan for the first facial transplants. Work in animal models was followed by practice on cadaveric models in humans. Important learning took place at this stage regarding both the appropriate methods of tissue retrieval and the optimal techniques for the attachment of donor tissues to the recipient.\textsuperscript{80}

Severe facial defects, like upper extremity defects, may be congenital or may result from burns, ballistic trauma, human or animal attacks, or diseases such as neurofibromatosis.\textsuperscript{81} Defects that may be regarded as severe generally involve functional deficits as well as cosmetic ones. Such defects may interfere with normal feeding, speech and the individual’s ability to use facial expressions to communicate with others.\textsuperscript{82} Defects may also interfere with the function of periorbital structures of the eye, such as voluntary and spontaneous or involuntary blinking. Involuntary blinking is particularly important as the absence of involuntary blink can lead to vision loss.\textsuperscript{83}

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For patients with severe defects, the standard treatment of autologous grafts produces only limited improvements, both functionally and cosmetically, with congenital or traumatic defects of the mid-face being especially problematic. Agich and Siemionow note that traditional methods typically result in skin discoloration, deforming contractures, and a visibly deformed appearance that is noticeable at a distance. While far from perfect, facial allografts produce far superior results, both esthetically and functionally. Functionally, patients who have previously needed gastrostomy tubes or who have been dependent on tracheostomies have been able to do without these interventions post-transplant. Significant improvements in speech intelligibility following facial VCA have also been demonstrated. In a recent report by Fischer et al., surveying a total of 29 face transplant recipients, improvements in the ability to smell, eat and feel (sensation) were seen in all, while breathing, speaking and facial expression showed benefit in a large majority. In a similar review of 28 recipients, Khalifian et al., report improved ability to eat, drink, speak, smell and smile in almost all patients.

Peter Butler, of London’s Royal Free Hospital, was the first surgeon to propose a program be established for conducting facial transplantations. His suggestion at a 2002 meeting of the British Association of Plastic Surgeons was heavily covered in the media, and elicited the expression of widespread and profound ethical concerns. Within a year, the Royal College of Surgeons announced at a public debate in the London Museum that it would be “unwise to proceed” until more research was done.

The first actual facial allograft, therefore, took place instead at Amiens, France. On November 27, 2005, a team led by surgeons Bernard Duvauchelle and Jean-Michael Dubernard transplanted a flap containing both the nose and mouth from a 46 year old brain-dead donor to a 38 year old recipient. The recipient had obtained her defect from dog bites while the patient was unconscious. Results

84Barker et al., “Research and Events Leading to Facial Transplantation,” 234; Wiggins et al., 3; Losee, Fletcher and Gorantla, 260.
85Agich and Siemionow, 708; Siemionow, 426; Zor, 157.
86Shanmugarajah, Hettiaratchy and Butler, 292–296; Siemionow and Ozturk, 254–255; Johnson and Corsten, 276; Infante-Cossio et al., e264; e268; Siemionow, 426; N. Roche et al., “Long-term multifunctional outcome and risks of face vascularized composite allotransplantation,” Journal of Cranio-facial Surgery 26, no. 7 (2015): 2039; Londono, Gorantla, and Badylak.
87Pomahac, Gobble and Schneeberger, 9.
were good and the graft functioned well for several years, though there were complications associated with side effects of immunosuppression. At 90 months post-transplant, problems with the graft were detected, and eventually necrosis of the lips and perioral area occurred, requiring surgical removal of those portions of the graft in May 2015. The patient subsequently developed an aggressive small cell lung cancer, leading to her death in April 2016.

Subsequent facial transplants have taken place in China, the United States, Spain, Turkey, Belgium, and Poland. France and the United States have had the largest number of cases thus far. The total number of procedures performed as of 2015 is thirty-four, with roughly half being partial face and the other half full face. Like the first patient, the cause of the defect in two other cases has been animal bites, while the most common form of trauma among facial transplant patients has been ballistic injuries. The average length of the transplant surgery has been 17.6 h. All of the recipients of facial grafts have had to deal with acute rejection and the side effects of immunosuppression. Along with the face-and-hand transplant recipient mentioned above and the first face transplant patient, four other facial transplant recipients have died. One was a Chinese victim of a bear attack who received a total nose, upper lip and parotid gland graft in 2006. The second was an HIV-positive recipient who later succumbed to a recurrence of cancer. The third was a Turkish patient who experienced organ failure and died following removal of the graft. The fourth resulted from suicide. Maintainance of the appearance of the graft has also been a concern, as over time changes have been

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95Siemionow, Gharb and Rampazzo, 635; Pomahac, Gobble and Schneeberger, 1.
97Pomahac, Gobble and Schneeberger, 1.
99Pomahac, Gobble and Schneeberger, 1–2.
100Siemionow, Gharb and Rampazzo, 635.
102Roche et al., “Facial Transplantation: History and Update,” 102.
103Wo, Bueno and Pomahac, 619.
observed that resemble rapid aging. On the whole, however, patients who have received facial tissue transplants have done well and are pleased with the results. Sensitivity and significant motor function have returned over time, with appropriate therapy.

### 2.3.3 Other VCA

A number of other types of vascularized grafts have been transplanted, with varying degrees of success. Early attempts with uterine transplantation in Saudi Arabia and Turkey did not lead to live births. More recently, a Swedish team has conducted a number of uterine transplants from living donors, with the hope of overcoming uterine-based infertility in the recipients. At six months post-transplant, seven of nine uteri remained viable. The capacity of these uteri to sustain a pregnancy was demonstrated by the birth of a baby boy in September 2014 to a 36-year-old woman who became pregnant via in vitro fertilization one year post-transplant. Four total live births had been reported as of mid-2015, with more expected later that year and in 2016.

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105 Sieminow, Gharb and Rampazzo, 634–636; Shanmugarajah, Hettiaratchy and Butler, 291–296. Londono, Gorantla and Badylak caution that an accurate picture of the quality of outcomes is difficult to obtain because a number of clinical failures “remain unpublished and unpublicized”.

106 Lengele, 515.

107 Like other forms of VCA, uterine transplantation is demanding for the patient and carries substantial risks. These burdens and risks include daily immunosuppression, potential effects on the in utero offspring, psychological and emotional complexities and expense. Further, because no nerves are reattached recipients do not experience movement of the fetus to the same degree that others do. See John A. Robertson, “Other women’s wombs: uterus transplants and gestational surrogacy,” *Journal of Law and Biosciences*, Advance Access (2016), doi:10.1093/jlb/lsw011.

Other types of VCA which have been attempted include tongue, lower extremities, abdominal wall, esophagus, larynx, penis and vascularized knees. Abdominal wall transplantation is actually one of the more common forms of VCA, along with upper extremity transplants and facial transplants. Abdominal wall transplantation frequently takes place in conjunction with intestinal transplantation, since the patients have often endured numerous previous abdominal surgeries which may result in multiple fistulae and other damage. Esophageal transplants are also often combined with the transplant of viscera.

Experience with several of these other forms of VCA raises concern. For example, the first total laryngeal transplant was explanted due to chronic rejection in 2012, fourteen years after transplant. Initial results were quite good, including voice quality and swallowing, but the graft went into serious decline in the twelfth year. Vascularized knee transplants have been unsuccessful on the whole, with Diefenbeck et al., reporting all six attempted grafts lost within fifty-six months of transplantation, including four from chronic rejection in spite of immunosuppression adherence. The double lower extremity transplantation performed by the team led by Cavadas required re-amputation when a lymphoproliferative disorder occurred and the patient chose to discontinue immunosuppression. While a later attempt at penile transplantation may be considered successful, in the initial case of human penile allotransplantation the recipient asked to have the graft removed within weeks, citing the psychological burden.

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2.4 Similarities and Differences in VCA and SOT

2.4.1 Similarities

Vascularized composite allotransplantation and solid organ transplantation share a number of similarities, as one might expect. For instance, in terms of surgical technique, both rely heavily on vascular anastomosis.\textsuperscript{116} SOT and VCA have a similar profile of surgical risks, such as complications arising from anesthesia and blood loss.\textsuperscript{117} The use of immunosuppressants to control rejection is also very similar, as is the importance of patient adherence to the immunosuppressive regimen and the need to monitor patients for side effects of these medications.\textsuperscript{118} Side effects include increased infection risk, the development of diabetes in many patients, and malignancies in some.\textsuperscript{119} Both VCA and SOT use similar methods and solutions to preserve the organs and tissues to be transplanted, and require a skilled team to work in a timely fashion to obtain grafts from donors.\textsuperscript{120}

Other similarities between SOT and VCA exist as well. Both must contend with the issue of donor consent and cope with a shortage of organs and tissues for transplantation.\textsuperscript{121} Likewise, both must address questions surrounding the appropriate allocation of the grafts that do become available, considering both matching (histological, size, etc.) and fairness.\textsuperscript{122} Both VCA and SOT recipients must be adequately informed prior to surgery and sufficiently supported after surgery, and both must contend with the psychological challenges of accepting the body part(s) of another as one’s own.\textsuperscript{123} Finally, both VCA and SOT are expensive treatments, far beyond the means of most people unless insurance or government funding is available.\textsuperscript{124}

\textsuperscript{116}Foroohar et al., 405; Shores, Imbriglia and Lee, 1863; Weissenbacher et al., 640.
\textsuperscript{117}Wiggins et al., 3–4.
\textsuperscript{118}Hautz et al., 3507–3509; Cavadas, Ibanez and Thione, 421; Morris et al., 114; 116–117; Shores, Imbriglia and Lee, 1862; Tintle et al., “Hand Transplantation,” 4.
\textsuperscript{119}Agich and Siemionow, 708; Gaby Doumit et al., “Pediatric Vascularized Composite Allotransplantation,” \textit{Annals of Plastic Surgery}, epub ahead of print, July 2014.
\textsuperscript{120}Schneebberger et al., 1089; Pomahac, Gobble and Schneebberger, 2; Dwyer et al., 285; Cetrulo Jr. and Kovach, 236.
\textsuperscript{122}Schneeburger et al., 1088; Murphy, Zuker and Borschel, 1450.
\textsuperscript{124}Kalliainen, 549; Siemionow, Gharb and Rampazzo, 636; Edwards and Mathes, 121.
2.4.2 Unique Features of Solid Organ Transplants

While solid organ transplantation shares a considerable number of features with vascularized composite allotransplantation, as detailed in the immediately preceding section, solid organ transplantation also differs from vascularized composite allotransplantation in certain ways. Some of those differences are related to the much longer clinical history and far greater scale of solid organ transplantation. As early as 1962, the number of kidney transplants being performed led to the first attempts at creating a fair system of allocation. Organ procurement organizations (OPOs) developed in various regions around the United States during the decade of the 60s, primarily in response to the rapid growth of cadaveric donor kidney transplantation. That growth was accelerated by the federal law in 1972 which created Medicare payment support for individuals with end stage renal disease. In 1984 the United States federal government passed the National Organ Transplant Act, which established the Organ Procurement and Transplantation Network (OPTN). OPTN in turn has contracted with the United Network for Organ Sharing (UNOS) a private, nonprofit organization, to oversee allocation through regional organ procurement organizations. In the intervening years, sophisticated systems of allocation have been developed. Allocation protocols differ by organ, and are determined in part by recipient characteristics and in part by donor characteristics.

VCA grafts were finally recognized as organs by the U.S. Department of Health and Human Services in July 2013. While this allows the allocation to be managed under OPTN, allocation protocols for facial and upper extremity grafts have yet to be developed and implemented. Currently, procurement for SOT and for VCA differs in several ways for a number of reasons, but primarily because the request for faces and limbs has not been fully integrated into the procurement system for solid organs. Suggestions for integration have been made, and focus on concerns

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about requests for VCA graft donations having a negative impact on the willingness of donors and donor families to donate solid organs. One common recommendation has been that requests for VCA grafts not take place until consent for solid organ donation has been obtained.130

Unlike VCA, solid organ transplants are considered standard therapy for certain disease states, and may therefore be covered by insurance or government funding. Because of this, SOTs are available to a far greater number of people. For example, according to OPTN, over 350,000 kidney transplants, 126,000 liver transplants and 57,000 heart transplants have taken place in the United States alone.131 By contrast, the total number of facial and upper extremity VCAs worldwide is approximately 200.132

Finally, SOTs are undertaken with the expectation that they will improve both the quality of life and the longevity of the patient, whereas VCAs are focused on quality of life only.133 This is true even for kidney and pancreas transplants, though they are occasionally described as focused on quality of life rather than the preservation or extension of life.134 There is ample evidence that those receiving kidney transplants live longer than those who remain on the waiting list.135 Pancreas transplantation also shows clear survival benefits over remaining on the list.136

130Rahmel, 174.
133Sayegh and Carpenter, 2762–2765; Ortega, 17–24.
134Hautz et al., 3504; V.C. Lees and S.J. McCabe, ‘‘The Rationale for Hand Transplantation,’’ Transplantation 74, no. 6 (2002): 749. Weissenbacher et al., 641, make a distinction between ‘‘life-saving’’ (heart, lung and liver) and ‘‘life-prolonging,’’ (kidney and pancreas), but note that VCAs are neither life-saving nor life-prolonging.
2.4.3 Unique Features of Vascularized Composite Allotransplantation

Given the brief clinical history of VCA, it is to be expected that many policies and procedures related to the practice are still in the process of formation and standardization.\(^{137}\) At the time of this writing, upper extremity transplantation has taken place at fewer than twenty transplant centers,\(^{138}\) while fewer than thirty facial transplants have been attempted.\(^{139}\) As noted earlier, systems of procurement and allocation protocols are still being developed, with current procurement and allocation aptly described by Rahmel as “ad hoc arrangements… similar to the situation in the early days of solid organ transplantation”.\(^{140}\)

Likewise still in the process of development are methods for identifying good candidates and determination of the best methods for supporting graft recipients.\(^{141}\) Debate continues about when it is most appropriate to offer VCA, since patients approached too soon may not have had the opportunity to adjust to their deficit as well as they might, while waiting longer may subject them to several painful surgeries or other treatments that would otherwise not be necessary.\(^{142}\) Even the technical sequence of the surgery itself is not yet fully established or agreed upon among the various surgeons and centers.\(^{143}\)

Those forms of VCA which involve skin are significantly different from SOT in three distinct ways. First, while both VCA and SOT recipients must contend with the psychological task of accepting the body part(s) of another as their own, the visible nature of grafts that include skin make the task both more urgent and less avoidable. Not only are the grafts involved in face and upper extremity transplants visible, but they are also tactile, both to the recipient and others. Visual and tactile encounters with the grafts are common both in clinical care and in activities of daily living, providing frequent reminders of the graft’s existence and eliciting concern

\(^{137}\)Diaz-Siso et al., 335.
\(^{138}\)Kumnig, Jowsey and DiMartini, 188.
\(^{140}\)Rahmel, 178.
\(^{141}\)Coffman and Siemionow, 184; Kumnig, Jowsey and DiMartini, 189–190; Tintle et al., “Hand Transplantation,” 2; 7; Siemionow and Ozturk, 255; Shores, Imbriglia and Lee, 1866; Foroohar et al., 405; 407–408; Errico, Metcalfe and Platt; Evans, 154; Klapheke et al., 453–457; Shores, 539.
\(^{142}\)Coffman and Siemionow, 182. The first emergency face transplant was reported in 2015 for a patient for whom other means of restoration were not feasible. The coincidental availability of a donor made this possible, and the outcome (especially the psychological outcome) will be watched carefully. Adam Majewski et al., “The First Immediate Face Transplant in the World,” Annals of Surgery, 263, no. 3 (2016): e36–e39.
\(^{143}\)Petruzzo and Dubernard, 248.
over how others may experience the graft and the recipient of the graft.\textsuperscript{144} As a consequence of the psychological challenges, both for the patient and close family members, substantial psychological and psychiatric support must be provided, particularly in the first post-surgical year.\textsuperscript{145}

The second way in which skin-involved VCA grafts differ from SOT grafts is in the immunological role of the skin. Of the components of a VCA graft, the skin is the most likely to be the site of acute rejection, followed by muscle, bone, cartilage and nerves.\textsuperscript{146} The presence of skin is thought to account for the much higher rate of acute rejection in upper extremity and facial VCAs, when compared to SOT. Ravindra et al., report that 85% of hand transplant recipients and almost 55% of face transplant recipients have episodes of acute rejection in the first year, compared to less than 15% of kidney transplant recipients.\textsuperscript{147}

The skin involved in VCA is also helpful, however, in identifying signs of acute rejection. Whereas the identification of acute rejection in SOT requires more complex analysis, such as elevation of creatinine in kidney transplants or reduced ejection fractions in heart transplants, the skin of VCA grafts demonstrates inflammatory responses for which patients themselves can monitor. Occasionally, skin inflammation in VCA recipients may be the result of something other than acute rejection and there is a need for better diagnosis and treatment of acute rejection in the field of VCA.\textsuperscript{148}

Still, the high degree of immunogenicity of skin allows it to serve a generally reliable sentinel function.\textsuperscript{149} Thus, while the rate of acute rejection episodes appears to be considerably higher in VCA, as compared to SOT, rejection episodes in VCA have tended to be more quickly identified and successfully treated. Some give credit to this sentinel function of skin for the fact that chronic rejection for immunosuppressant-compliant patients has been rare in VCA, compared to SOT.\textsuperscript{150} Others, however, have questioned this connection, noting that chronic rejection in VCA can occur without changes to the skin and they have recommended routine

\textsuperscript{144}Evans, 154; Errico, Metcalfe and Platt; Foroohar, 407; Kumnig, Jowsey and DiMartini, 189–193; Coffman and Siemionow, 184.; Morris et al., 117; Lengele, 508.
\textsuperscript{145}Roche et al., 6.
\textsuperscript{146}MacKay, Nacke, and Posner, 81. While traditionally thought to be more antigenic than other tissues, Fadi Issa argues that skin is actually no more antigenic but more susceptible to rejection for other reasons. See “Vascularized composite allograft-specific characteristics of immune responses,” Transplant International Epub (2016), doi:10.1111/tri.12765.
\textsuperscript{147}Ravindra et al., 1.
\textsuperscript{149}Alexander et al., 62.
\textsuperscript{150}Siemionow, Gharb and Rampazzo, 634–636; Errico, Metcalfe and Platt; Murphy, Zuker, and Borschel, 1451; Diaz-Siso et al., 333–335; Foroohar et al., 408; Shores, Imbriglia and Lee, 1863; Tintle et al., “Hand Transplantation,” 4–5; Evans, 153.
biopsies to rule out chronic rejection whether or not signs of acute rejection are seen.\textsuperscript{151}

The third way in which VCAs involving skin are different from SOTs is that the pigmentation, size, age and gender of the donor become far more relevant. Matching donor and recipient in SOT and VCA considers blood type and HLA, but in visible VCA matching must also consider how the facial graft or limb will look cosmetically, as this may influence the patient’s ability to psychologically accept the graft. Such considerations must be kept in mind by the procurement staff and the suitability of a donor match is typically evaluated by the surgical team before the donation is accepted.\textsuperscript{152}

Because vascularized composite allotransplantation involves the transplantation of multiple tissue types (e.g., skin, fat, muscle, bone, nerves, ligaments, etc.) as a single unit, it differs from solid organ transplantation which is concerned with a unit that is predominantly one type of tissue. This is significant because, as Zor points out, various tissue types show “different functional and immunologic characteristics”.\textsuperscript{153} Success in VCA requires all the tissue types to be tolerated immunologically and all to regain some degree of function in the recipient.

VCA transplant recipients tend to be healthier overall than recipients of SOT. VCA candidates often suffer from psychological as well as physical injuries, but do not have the metabolic or physiological deficits that make others candidates for SOT.\textsuperscript{154} The fact that VCA recipients have been both healthier and younger on the whole than SOT recipients has likely contributed significantly to fewer and less severe complications being experienced in VCA recipients than in SOT recipients.\textsuperscript{155}

While they may be considered less than ideal, alternative treatments do exist for VCA candidates. Autologous flaps, tissue expansion, standard skin grafting and artificial dermal xenografts exist as alternatives for the repair of facial defects.\textsuperscript{156} It should be noted that non-VCA treatment for major facial tissue defects typically involves multiple surgeries which take place over an extended period of time and


\textsuperscript{153}Zor, 157.

\textsuperscript{154}Kumnig, Jowsey and DiMartini, 189; Coffman and Siemionow, 181–182; Tintle et al., “Hand Transplantation,” 7; Hautz et al., 3505; Weissenbacher et al., 641; Siemionow, Ghard and Rampazzo, 638; Murphy, Zuker, and Borschel, 1451; Foroohar et al., 408; Shores, Imbriglia and Lee, 1865.

\textsuperscript{155}Pushpakumar et al., 955; Barker et al., “Research and Events,” 239; Shores, Imbriglia and Lee, 1863; Foroohar et al., 408.

\textsuperscript{156}Coffman and Siemionow, 182; Zor, 156.
still yield cosmetic and functional results that may be considered inferior to what is possible with VCA.\textsuperscript{157}

For upper extremity VCA candidates, prostheses are an obvious and common alternative. Prostheses are fitted following the necessary residual limb reconstruction and sufficient time for healing of the soft tissue. Short-term rehabilitation follows,\textsuperscript{158} including both training in the use of the prosthesis and psychological support. Despite the discomfort and other limitations often associated with upper extremity prostheses, they permit good motor function with far less risk and cost than VCA.\textsuperscript{159} Current research in prosthetics holds out the promise of restoring sensation as well as motor function.\textsuperscript{160} However, as prosthetics become more sophisticated, the difference in costs between prostheses and VCA is likely to be significantly reduced.

Attitudes toward VCA and SOT are also dissimilar. This is true of physicians as well as of the general public. Physicians remain somewhat skeptical of the field of VCA, although some improvement is being seen.\textsuperscript{161} With regard to SOT, physicians show a much higher willingness to register as donors than do members of the general population.\textsuperscript{162} By contrast, the general population is much more willing to consider face transplants than are burn and plastic surgeons involved in facial reconstruction.\textsuperscript{163}


\textsuperscript{158}Salminger et al., report an average of a mere 10–20 h of therapy in total for prostheses.

\textsuperscript{159}Hautz et al., 3505; Tintle et al., “Hand Transplantation,” 6; Errico, Metcalfe and Platt; Klapheke et al., 457; Pribaz and Caterson, 99–107; Jensen et al., 2127; Chang and Mathes, 553–554; Salminger et al., 2.


A comparative international study of attitudes toward donation and toward accepting a facial graft demonstrated substantial differences between “western” countries (U.S., United Kingdom, France, Australia and Brazil) and “eastern” countries (Iraq, Japan, Singapore, Taiwan and Korea). Overall, the respondents from the “western” countries indicated more willingness to both donate and accept facial grafts. In a recent U.S. study undertaken to compare the willingness of the general public to donate or receive either a VCA graft or an SOT graft, there was a consistent pattern of greater reluctance regarding both donation and reception when VCA was under consideration. 85% were willing to receive a kidney, while only 60% were willing to receive a hand and just 50% were willing to receive a facial transplant. Attitudes toward donation also differed significantly when comparing VCA and SOT. More than 75% were willing to donate kidneys, livers and hearts upon death, but only 55% were willing to donate a hand and 44% were willing to donate a face. The support for insurance or government programs as sources of payment was also lower for VCA than for SOT.

A difference between VCA and SOT with particularly profound ethical implications is that while SOT is directed at preserving and extending life, and has been demonstrated to do so, VCA is aimed at improving quality of life and, due to the risks associated with surgery and prolonged use of immunosuppressants, carries a significant risk of shortening the patient’s life. Susceptibility to various infections is one risk associated with conventional immunosuppression. Indeed, in spite of prophylaxis, the majority of VCA recipients have developed at least one opportunistic infection, whether viral, bacterial or fungal. Still other risks of immunosuppression include metabolic changes leading to renal compromise or diabetes mellitus, hypertension, gastrointestinal problems, and an increased

(Footnote 163 continued)

Toward Vascularized Composite Allotransplantation of the Hands and Face in an Urban Population,” Vascularized Composite Allotransplantation 1, no. 1–2(2014): 25–28. It is acknowledged that these comparisons sometimes depend on willingness to donate, contrasted with willingness to receive. While there is nearly always a discrepancy between the rates, with willingness to donate generally lagging behind willingness to receive, in this instance this only emphasizes the disparity between physicians and the general public.

167Hautz et al., 3504–3509; Evans, 154–159; Shores, Imbriglia and Lee, 1865; Breidenbach et al., 1046; Siemionow and Ozturk, 256; Dickenson and Hakim, 513; Murphy, Zuker and Borschel, 6; Kumnig, Jowsey and DiMartini, 150; Coffman and Siemionow, 184–185.
168Pomahac, Gobble and Schneeberger, 11.
likelihood of developing certain cancers, particularly non-Hodgkin lymphoma, Kaposi’s sarcoma, nonmelanoma skin cancers, anogenital cancers and Hodgkin lymphoma.169

A final difference between VCA and SOT, which also has considerable ethical import, is that unlike kidneys, hearts, lungs or livers which begin to function almost immediately following transplantation, meaningful functional recovery in VCA requires intensive and time-consuming therapy.170 While thermalgesic and discriminatory sensitivity develop more or less spontaneously within the first six months, motoricity is recovered over a far longer period, and only with physiotherapy which begins quite soon after surgery.171 As Kumnig, Jowsey and DiMartini note, this therapy may yield little immediate functional or sensory improvement, thereby causing discouragement in patients.172 Compliance with both immunosuppressive medication and with rehabilitation has been problematic for some VCA patients, perhaps as a result of such discouragement.173

One factor in the length of time it takes for motor function and sensation to recover is the slow progress of reinnervation.174 Pomahac, Gobble and Schneeberger report nerve regeneration in upper extremity transplantation taking from six to nine months in transplants near the wrist level, and increasingly longer as the site of attachment moves further up the extremity. Various aspects of sensory and motor reinnervation develop over time in both facial and upper extremity transplants and fall short of complete restoration.175

169Coffman and Siemionow, 182–183; Hautz et al. 3506–3507; Weissenbacher et al., 641–642; Tintle et al., 4–6 “Hand Transplantation,”; Errico. Metcalfe and Platt; Siemionow, Gharb and Rampazzo, 634–638; Shores, Imbriglia and Lee, 1864–1865; Siemionow and Ozturk, 256; Evans, 153–154; Diaz-Siso et al., 335; O’Neill and Godden, 444; Pomahac, Gobble and Schneeberger, 12; Edwards and Mathes, 120; Wo, Bueno and Pomahac, 619. The small cell lung cancer which caused the death of the first face transplant patient may or may not have been caused by immunosuppression. It is more likely the result of her heavy smoking, but the cause cannot be scientifically proven one way or the other.

170Tintle et al., “Hand Transplantation,” 6; Amer et al., 42; Murphy, Zuker and Borschel, 4; Dubernard et al., 2459; Ericka Bueno et al., “Rehabilitation following hand transplantation,” Hand 9 (2014): 9; 14; Shores, Brandacher and Lee.


172Kumnig, Jowsey and DiMartini, 189.


174Siemionow, Gharb and Rampazzo, 634; Shores, Imbriglia and Lee, 1863–1864; Foroohar et al., 408; Petruzzo and Dubernard, 413; Dubernard et al., 2453–2454; Petruzzo et al., 237; Shanmugarajah, Hettiaratchy and Butler, 294–295; Breidenbach et al., 1039; Herzberg et al., 116; Hodges, Chesher and Feranda, 389–392; Dixon et al., 152–170; Infante-Cossio et al., e268; Ninkovic et al., 459–460.

The slow progress of nerve regeneration is a major factor in the decision by most upper extremity VCA programs to focus on below-the-elbow transplantation, and in the limited interest thus far in attempting lower extremity transplants. Promising work is being conducted, primarily in non-human models, on strategies to promote more rapid nerve regeneration. Schwann cells are a major focus, but mesenchymal and stromal cells are also being investigated as resources to promote nerve repair. Induced pluripotent stem cell-derived Schwann cells have the added advantage of being native to the recipient and thus not causing a rejection response. Schwann cells are otherwise highly immunogenic. If nerve regeneration can occur more rapidly, recipients may be encouraged by the progress and compliance with medication and therapy regimens may improve.

2.5 Practical and Ethical Concerns in the Field of Vascularized Composite Transplantation

The practical and ethical concerns associated with VCA are frequently related. Procedural, technical and medical issues raise ethical concerns, and the resolution of those issues would alleviate many of the concerns. For example, significant reduction in the risk and burden profile would lessen the concern that has arisen from subjecting patients to those risks and burdens in a surgery that is not necessary to preserve or extend life. While the prospects of such improvements can and should raise hope, they cannot be used to justify the practice of human vascularized composite allotransplantation now. Justification for the practice today depends on the conditions now existing. What follows is a survey of the practical and ethical concerns, as they exist at present.

2.5.1 Immunological Concerns

2.5.1.1 Rejection and the Potential for Graft Loss

Rejection of transplanted tissue is a central concern of transplantation generally, though the nature, frequency and extent of rejection vary according to the kind of
organ or tissue that is transplanted. As discussed above, it was not until the first effective immunosuppressants were developed that solid organ transplantation became feasible. Because of the high level of immunogenicity of skin, the feasibility of VCA involving skin did not occur until second and third generation immunosuppressants became available.

Rejection may be hyperacute, acute or chronic. Hyperacute rejection appears within minutes to hours following anastomosis. Acute rejection takes place days to months after transplantation. Chronic rejection is a slowly developing condition that damages the allograft by means of vasculopathy and fibrosis, leading to loss of function. The first line of defense against rejection is blood-type and HLA matching of donor and recipient, but complete matches are seldom feasible.

Even with good adherence in the use of immunosuppression, rejection may still take place. In VCA, there have been high rates of acute rejection, especially within the first year. Lantieri calls it “almost inevitable”. In upper extremity transplantation, one source reports 85% of recipients experience at least one episode of acute rejection, while 56% experience more than one episode. Acute rejection in upper extremity and facial VCA typically manifests as a rash on the skin and, in the case of facial transplants, the mucosa of the mouth and nose. These acute rejection episodes have been quickly identified, due to the sentinel role of the skin, and have responded well to treatment, typically resolving within a short time without apparent lasting damage to the graft tissue. Early detection, by simple visual inspection or by means of dermoscopy, is most likely a reason for good results of treatment for acute rejection, and the generally good health of VCA patients may also factor in.

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180 Amer et al., 40.


182 Heeger and Dinavahi, 376; Ninkovic et al., 455.

183 Barker et al., 239; Diaz-Siso et al., 333–334; Petruzzo and Dubernard, 248; Petruzzo et al., 810; Siemionow and Ozturk, 256; Weissenbacher et al., 643; Lantieri, 253; Lantieri et al., 372.

184 Lantieri, 253.

185 MacKay, Nacke and Posner, 81.


187 Lengele, 511–515; Yi and Guo, 177; Shanmugarajah, Hettiaratchy and Butler, 295; Pomahac, Gobble and Schneeberger, 10.

Chronic rejection in SOT is manifested by vasculopathy and fibrosis, with the organ function declining.\textsuperscript{189} In several cases of human upper extremity VCA there have been signs of chronic rejection, which often leads to graft loss in SOT.\textsuperscript{190} Signs of chronic rejection have also been present in nonhuman primate VCA models, despite the use of immunosuppressants.\textsuperscript{191} Still, chronic rejection in VCA is rare, compared to the rates seen in SOT. However, the evidence for chronic rejection is uneven, with centers such as Lyon and Innsbruck reporting none, while the University of Louisville Hand Transplant Program reported evidence in five of six recipients at one point, including one case that led to graft loss.\textsuperscript{192} The overall low rate of chronic rejection may be attributed to the relatively short history of VCA, and there is some expectation that chronic rejection will develop eventually in most VCA grafts.\textsuperscript{193} Thus far, graft loss has occurred in six upper extremity transplants in the U.S. and Europe, with four of the six being necessary because of rejection. Seven upper extremity transplants have had to be amputated in China, but problems with the availability of immunosuppression are thought to account for this.\textsuperscript{194}

Graft loss would inflict additional burdens and risks upon both upper extremity and face transplant patients.\textsuperscript{195} There would be the necessary surgery to remove the graft, with risks related to anesthesia and a heightened potential for post-surgical infections. Upper extremity patients who rejected the graft and required amputation would need time to heal before they could be fitted anew with prosthetic limbs, creating a period of increased dependency on others.\textsuperscript{196}

For recipients of facial transplants, graft loss would be even more devastating.\textsuperscript{197} Whereas the upper extremity patient who lost a graft might reasonably be assumed to be able to return to essentially the same condition he or she was in prior to transplant, several have noted the strong possibility that loss of a facial transplant graft would leave patients even worse off than they were before transplant.\textsuperscript{198} This would certainly be true for those who have undergone total rather than partial face transplantation, and must be weighed against the possibility that a total face

\textsuperscript{189}Inal, 8.
\textsuperscript{190}Barker et al., 240; Murphy, Zuker and Borschel, 1451; Ravindra et al., 2; Lees and McCabe, 751; Tintle et al., “Hand Transplantation,” 5; Shores, Imbriglia and Lee, 1862–1863; Shanmugarajah, Hettiaratchy and Butler, 295.
\textsuperscript{191}Mundinger and Drachenberg, 311.
\textsuperscript{192}Mundinger and Drachenberg, 310.
\textsuperscript{193}Pomahac, Gobble and Schneeberger, 10; Morelon, Kanitakis and Petruzzo, 857.
\textsuperscript{194}MacKay, Nacke and Posner, 82.
\textsuperscript{195}Morris et al., 119; Lees and McCabe, 750; Kalliainen, 550; Hautz et al., 3507.
\textsuperscript{196}Petruzzo and Dubernard, 249–250; Shores, Imbriglia and Lee, 1864.
\textsuperscript{197}Siemionow and Ozturk, 257.
\textsuperscript{198}Edwards and Mathes, 119; Kalliainen, 551; Strong, 1115; Agich, 135–136; Coffman and Siemionow, 182; Murphy, Zuker and Borschel, 1450; Strong, 1115–1116; Edwards and Mathes, 119.
transplant may give a better functional and esthetic outcome. Facial graft loss would require multiple procedures to repair the wound and would yield a less satisfactory outcome than pre-transplant interventions. Concerns have increased about chronic rejection in facial allotransplantation since the first report of findings in 2015.

2.5.1.2 Immunosuppression

Because rejection interferes with graft function and can lead to graft loss, immunosuppression is implemented. Immunosuppression typically takes place in three stages: the induction phase, the maintenance phase, and the rescue phase. The induction phase prepares the recipient to receive foreign tissue, which will otherwise provoke a major immune reaction. Induction involves high doses of immunosuppressives. Due to the undesirable side effects of the immunosuppressants, particularly at higher doses, the effort is made as soon as possible after surgery to shift to a lower dose maintenance phase. When there are signs of rejection, a return to higher dose immunosuppression for a limited time constitutes the rescue phase.

Immunosuppression regimens in both SOT and VCA vary because research has yet to clearly identify best practices, even in renal transplantation, the form of SOT with the longest history and greatest number of transplants attempted. Most often, however, a combination of an induction antibody, calcineurin inhibitor, an antiproliferative drug and a steroid is used. Commonly used immunosuppression in VCA includes rituximab, tacrolimus, mycophenolate mofetil and prednisolone. Medications are usually taken orally or intravenously but topical application is also used, especially in acute rejection where skin is involved, and

200O’Neill and Godden, 444.
204Morelon, Kanitakis and Petruzzo, 858; Leonard et al., 268; Siemionow and Ozturk, 256; Leonard, Kurtz and Centrulo, Jr., 645–646; Murphy, Zuker and Borschel, 3; Tintle et al., “Hand Transplantation,” 3–4; Infante-Cossio et al., e268; Lantieri, 253; Lengele, 511; Shores, Imbriglia and Lee, 1862–1863; Hautz et al., “World Experience,” 429; Breidenbach et al., 1045; Schuind et al., 375; Leonard et al., 268; Karoline Edtinger et al., “Current Status of Vascularized Composite Tissue Allografting,” *Burns and Trauma* 2, no. 2 (2014): 54–55; Khalifan et al., “Facial Transplantation,” 2153.
this therapy has proven effective.\textsuperscript{205} Other forms of immunosuppression used in VCA include irradiation of the graft, extracorporeal photopheresis, IgG infusion and donor iliac crest bone marrow cell infusion.\textsuperscript{206}

While useful for preventing or delaying rejection, immunosuppression does carry with it substantial risk of complications, such as opportunistic infections, malignancies, new onset diabetes after transplant, nephrotoxicity, hypertension, neurotoxicity and other problems.\textsuperscript{207} Some of these, either singularly or in combination, may in time lead to the death of the recipient. A recent study out of Poland showed significant pathological changes in cardiac structures in a small sample of hand transplant recipients. These changes included arterial wall changes and endothelial dysfunction. The researchers concluded that hand transplantation puts recipients at higher risk for cardiovascular disease.\textsuperscript{208} Research continues into ways to avoid, withdraw or minimize immunosuppression, so that side effects may be avoided or lessened, with a focus on single agent maintenance therapy and steroid-free immunosuppression.\textsuperscript{209} Still, at present withdrawal of immunosuppressive therapy predictably results in the loss of the graft.\textsuperscript{210}

While the side effects of the immunosuppressants used in VCA are predominantly negative, there is an important exception. Calcineurin inhibitors (CNIs) interfere with the function of an enzyme that is involved in T-cell production. The two CNIs employed in transplant immunosuppression are ciclosporin and tacrolimus. Tacrolimus is the more popular of the two, despite the fact that it is more likely to contribute to the development of diabetes post-transplant.\textsuperscript{211}

\textsuperscript{205}Siemionow and Ozturk, 256; Yi and Guo, 178; Petruzzo and Dubernard (2011), 248; Leonard et al., 268.
\textsuperscript{206}Saami Khalifian et al., “Facial Transplantation,” 2153. Kaufman et al., “Immunobiology in VCA,” suggest that vascularized bone marrow offers “prolonged survival” of grafts in animal models, though the mechanism is not yet proven.
\textsuperscript{207}MacPhee and van Gelder, 254; Leonard et al., 270; Tintle et al., “Hand Transplantation,” 4; Lantieri, 252; Bohdan Pomahac et al., “Three Patients with Full Facial Transplantation,” The New England Journal of Medicine 366, no. 8 (February 23, 2012): 719–721; Yi and Guo, 177; Lantieri, 252; Shanmugarajah, Hettiaratchy and Butler, 295; Barker et al., “Research and Events,” 240; Lantieri et al., 375; Siemionow and Ozturk, 256; Leengele, 517; T. Hautz et al., “How Reconstructive Transplantation is Different,” 3508; Shores, Imbriglia and Lee, 1864; Hautz et al., “World Experience,” 429; Foroohar et al., 406; Petruzzo and Dubernard (2011), 249; 252; Edwards and Mathes, 120; Harriet O’Neill and Daryl Godden, “Ethical Issues of Facial Transplantation,” British Journal of Oral and Maxillofacial Surgery 47 (2009): 444; Chang and Mathes, 554; Alexander et al., 61; Morelon, Kanitakis and Petruzzo, 858; Errico, Metcalfe and Platt; Roche et al. 8.
\textsuperscript{209}Siemionow and Ozturk, 257; Siemionow, Gharb and Rampazzo, 637.
\textsuperscript{210}Heeger and Dinahavi, 376; Ravindra, Xu and Ilstadt, 3501; Shores, Imbriglia and Lee, 1865; Pomahac et al., 715; Breidenbach et al., 1046; Ninkovic et al., 455; Foroohar et al., 406–407; J.E. Janis et al., “Management of Steroid-resistant Late Acute Cellular Rejection Following Face Transplantation: A Case Report,” Transplantation Proceedings 47 (2015): 224–225.
\textsuperscript{211}MacPhee and van Gelder, 251–255, SMEETS et al.
particularly popular with VCA transplant teams because in addition to suppressing the mechanisms of rejection, it also promotes more rapid nerve regeneration.\textsuperscript{212} When the side effects of tacrolimus on the renal system are judged too great or there are signs of vasculopathy, a switch may be made to sirolimus. Sirolimus is not a CNI but has a similar suppressive effect.\textsuperscript{213}

\subsection*{2.5.1.3 Tolerance Induction}

Minimization of the use of immunosuppression, in order to lessen the toxic side effects, will continue to be a focus in both VCA and SOT. Ideally, transplant teams would like to eliminate the need for immunosuppression altogether.\textsuperscript{214} One avenue to minimization and perhaps even the elimination of immunosuppressants is tolerance induction.\textsuperscript{215} Heeger and Dinahavi define tolerance as a state in which “the immune system does not respond to the transplant but is otherwise fully functional in the absence of immunosuppression”.\textsuperscript{216} Ravindra et al., are correct in saying that if and when tolerance induction in humans is accomplished, it will be “transformational” for the field of transplantation.\textsuperscript{217} This is especially true for VCA, since the procedure does not offer the benefit of extending life, as in the case of SOT. Some have even described tolerance induction as “a necessity for wider application of” certain forms of VCA.\textsuperscript{218}

A variety of means of inducing tolerance have been imagined and several are being studied. It has been hoped that the inclusion of bone in some VCAs might prompt chimerism, or a hybrid immune system, as currently takes place with bone marrow transplantation. Some have gone further by using donor bone marrow infusion with VCA patients in an attempt to produce tolerance. While tolerance per se has not been achieved, it has permitted low dose tacrolimus monotherapy.\textsuperscript{219} Such infusions carry their own risks, however, including graft versus host disease.\textsuperscript{220} Huang et al., list several other possible methods of inducing tolerance,

\textsuperscript{212}Siemionow, Gharb and Rampazzo, 1885; Dwyer et al., 286; Morelon, Kanitakis and Petruzzo, 858.
\textsuperscript{213}Petruzzo et al., “First Human Face Transplant,” 240.
\textsuperscript{215}Pushpakumar, 956; Lantieri, 253; Shanmugarajah, Hettiaratchy and Butler, 296; Lengele, 514–515; Heeger and Dinahavi, 385; Huang et al.; Murphy, Zuker and Borschel; Edtinger et al., 56–57.
\textsuperscript{216}Heeger and Dinahavi, 385.
\textsuperscript{217}Ravindra et al., 4. Errico, Metcalfe and Platt describe it as “the holy grail of transplantation surgery”.
\textsuperscript{219}Leonard et al., 270; Ravindra et al., 6; Tintle et al., “Hand Transplantation,” 5.
\textsuperscript{220}Leonard et al., 5; Lantieri, 253; Leonard, Kurtz and Cetrulo, 647; Ravindra, Xu and Ilstadt, 3501.
including T-cell depletion, costimulation blockade and the infusion of mesenchymal stem cells from the donor or even from a third party.\textsuperscript{221}

Some animal studies have shown promise. Work with both small animals (mice and rats) and large animals (canines, swine and non-human primates) continues. An immunoablative approach, in which the recipient undergoes bone marrow transplantation, has produced chimeric tolerance in some animal models.\textsuperscript{222} Thus far, however, tolerance induction in VCA has repeatedly been achieved in small animals, but far less often in larger ones.\textsuperscript{223}

There have been SOT patients who have demonstrated spontaneous tolerance. A number of the very early renal transplant recipients maintained their grafts after ceasing immunosuppression, in one case for as long as thirty years. A liver recipient with apparent tolerance has retained the transplant for sixteen years, immunosuppressive-free. In 1992, donor leukocyte chimerism was detected in the kidney transplant patients who had demonstrated spontaneous tolerance.\textsuperscript{224} Yet, while the animal research is promising and the instances of human graft tolerance in some SOT recipients are suggestive, routine induction of tolerance in human SOT or VCA remains elusive.

\section*{2.5.2 Psycho-Social Issues}

\subsection*{2.5.2.1 Patient Motivation}

The nature and extent of motivation for undergoing VCA is assessed as part of the screening process. For facial transplant candidates, motivations are often grounded in both functional limitations and aesthetic concerns. A desire to be able to eat and breathe normally, to regain olfactory sensation, and to be able to communicate with facial expression is often voiced, as is the desire for aesthetic restoration that will

\begin{itemize}
  \item \textsuperscript{221}Huang et al., 3\textendash{}4. See also Ravindra et al., 4\textendash{}8.
  \item \textsuperscript{222}Heeger and Dinahavi, 385.
  \item \textsuperscript{223}Ravindra et al., 3\textendash{}4; Leonard et al., 5. Success has been seen in human renal transplant patients, according to Leonard et al., 270. Signs of progress are being seen quite recently, however. See D.A. Leonard et al., “Vascularized Composite Allograft Tolerance Across MHC Barriers in a Large Animal Model,” \textit{American Journal of Transplantation} 14, no. 2 (2014): 343\textendash{}355; R. Jindal et al., “Spontaneous Resolution of Acute Rejection and Tolerance Induction with IL-2 Fusion Protein in Vascularized Composite Allotransplantation,” \textit{American Journal of Transplantation} 15, no. 5 (2015): 1231\textendash{}1240.
\end{itemize}
allow for more normal social interaction.\textsuperscript{225} For some upper extremity transplant candidates, motivation may be focused on gaining the ability to perform occupational tasks or activities of daily living. For others, the chief motivation is based in aesthetic or bodily integrity concerns, or a desire for sensation.\textsuperscript{226} Martin Klapheke and colleagues found that a number of individuals who had experienced upper extremity loss had continued to participate in a wide range of physical activities, from scuba diving and martial arts to sewing and playing a guitar, yet these persons still expressed interest in upper extremity transplantation.\textsuperscript{227}

However, others who by reason of the extent of defect would be candidates for VCA are not interested, even before they are made aware of the burdens and risks involved.\textsuperscript{228} Most persons using upper extremity prostheses are not fully satisfied with them. Common complaints include the weight, the functional limitations, and especially the lack of sensation, with thirty percent of upper limb amputees rejecting the use of prostheses, with the rate of prosthesis rejection increasing as the level of amputation becomes more proximal.\textsuperscript{229} Nonetheless, dissatisfaction with prostheses does not translate directly into a willingness to undergo VCA.

It remains unclear why some with major facial defects or missing limbs are motivated to pursue VCA while others are not. Some people find conventional methods of reconstruction acceptable and are able to adapt well physically and psychologically, while others of equal or lesser defect do not.\textsuperscript{230} The subjective perception of the defect and its effect on quality of life seem to matter more than an objective evaluation of the extent of the defect.\textsuperscript{231}


\textsuperscript{226}Kumnig, Jowsey and DiMartini, 189: Hautz et al., “World Experience,” 425; Ninkovic et al., 463. Salminger et al., point out that unilateral amputees tend to be motivated primarily by psychological issues, while bilateral amputees are more interested in improved functionality.

\textsuperscript{227}Klapheke et al., 455.

\textsuperscript{228}Alexander et al., 61.

\textsuperscript{229}Tintle et al., “Hand Transplantation,” 1; Jenson et al., 2127; Klapheke et al. 455–456; Hautz et al. 3505. Tintle et al., “Traumatic and Trauma-Related Amputation,” 2939–2940, note that transradial amputees reject prostheses only 20% of the time or less.


Subjective evaluations may also change over time.\textsuperscript{232} Renshaw et al., contend that for those whose defect is the result of trauma, distance in time from the traumatic event may play a significant role in the level of motivation. They cite research that indicates people are more willing to take risks to erase a loss than they are to achieve a gain. When the traumatic event is recent, a person is more likely to view VCA as a means to erase the loss. After time passes, however, and the person makes some adaptations, he or she is more likely to view VCA as a means to gain a better life.\textsuperscript{233} Based on this analysis, it may be wise to allow time following injury for the individual with the defect to find a stable level of motivation.\textsuperscript{234}

That the degree of defect does not seem to be determinative suggests that repair of the defect by means of VCA may not be the only way to address and potentially remedy the suffering that motivates individuals to accept the burdens and risks associated with VCA. Research is available regarding the factors that contribute to the ability to adapt and possible methods for promoting adaptation and acceptance, and this research should be more fully integrated into VCA research programs.\textsuperscript{235} A number of models and methods have proven helpful to some patients with visible difference, either through attempts to desensitize the disfigured person to the reactions of others or through the development of new social skills, or some combination of both approaches. As Norman and Moss note, while further research into the efficacy of various methods is needed, “the techniques themselves are still important”.\textsuperscript{236} Organizations, such as Changing Faces in the United Kingdom and similar groups elsewhere, may have resources and experience that can be considered in the process of informing candidates for VCA of their alternative treatment options.\textsuperscript{237}

Also, in light of the fact that degree of defect does not correlate with motivation, some have expressed concern that motivation may at times verge on desperation, and thus compromise the ability of the VCA candidate to fully understand and

\textsuperscript{232}Morris et al., 115.
\textsuperscript{233}Renshaw et al., 864.
\textsuperscript{236}Norman and Moss.
\textsuperscript{237}Information about Changing Faces is available at \url{https://www.changingfaces.org.uk/Home}. 
rationally weigh the information provided about the procedure, particularly the information regarding benefits, burdens and risks.\textsuperscript{238} As Bradbury puts it, patients may listen “through a filter of hope and distress”.\textsuperscript{239} The powerful emotions that may be experienced by those who learn of the VCA option have been described in the literature.\textsuperscript{240} Motivation levels that are extreme do raise concern. Coffman and Siemionow report that ideal patients are less socially avoidant and tend to believe that disfigurement does not inevitably preclude happiness.\textsuperscript{241}

2.5.2.2 Identity

Upper extremity and facial VCA have raised concern and debate over the psychological impact of the transfer of visible tissue and its effect on the recipient’s sense of identity. While more of the concern and debate has centered on facial transplantation, and reasonably so given the greater link between personal identity and the face,\textsuperscript{242} upper extremity transplantation must also wrestle with the implications of “what it means to… wear and use someone else’s hand”.\textsuperscript{243} Both limbs and faces which are transplanted are readily recognizable as “other”.\textsuperscript{244}

The role of identity, or more precisely the patient’s ability to identify with the donor limb, came to the fore early in the history of clinical limb transplantation. The first recipient of a hand eventually asked for it to be removed, claiming a sense of alienation from it.\textsuperscript{245} It has since become clear that integrating the graft into one’s sense of self is no easy task. It involves adjustment over time that is mediated in part through the patient’s interaction with others and with objects.\textsuperscript{246} Psychological screening to determine whether or not a candidate is likely to be able to integrate the donor limb into his or her sense of self has become standard.\textsuperscript{247} Most problems with


\textsuperscript{239}Bradbury, 195.

\textsuperscript{240}Klapheke et al., 455.

\textsuperscript{241}Coffman and Siemionow, 374. See also Furr et al., 562–563.

\textsuperscript{242}Francoise Baylis, “A Face is Not Just Like a Hand,” \textit{The American Journal of Bioethics} 4, no. 3 (2004): 30–32.

\textsuperscript{243}Kumnig, Jowsey and DiMartini, 189.

\textsuperscript{244}Lengele, 518; Catsanos, Rogers and Lotz. See also Jenny Slatman, \textit{Our Strange Body: Philosophical Reflections on Identity and Medical Interventions} (Amsterdam: Amsterdam University Press, 2015): esp. 76–82 and 110–114.


\textsuperscript{246}Errico, Metcalfe and Platt; Crawford, 20.

\textsuperscript{247}Chang and Mathes, 556–557.
the ability to identify with the engrafted limbs occur early on, before there is significant return of sensation or motor function. Improvement in function promotes acceptance of the limb as part of the subject, rather than as an object. As time passes and function develops, identification improves and in hand transplantation overall it has been excellent. 248

Kiwanuka et al., in their excellent review of the history of ethical debate related to facial VCA, note that much of the early concern regarding face transplantation had to do with the prospect of identity transfer between the donor and recipient.249 One commentator even suggested that facial transplantation would simply be “to replace one disfigurement by another”.250 The level of concern in this area has decreased substantially with clinical experience, as the degree of resemblance between donor and recipient has not been great.251 Adaptation to the facial graft and identification with the graft has been very good overall.252 Part of the reason may be that recipients typically feel they have lost their former identity through the defect and have been alienated from their disfigured pre-transplant faces in this respect. Thus, though the graft is not a restoration of the original face, it is a restoration of a face and replaces the identity that was lost.253

Slatman and Widdershoven insightfully observe that the process of identification with the graft is “not merely subjective, but rather intersubjective.” That is to say, the patient’s ability to identify with the graft is determined in part by the response to the graft by others, especially those in close relationship with the recipient. Loved ones also must adjust to the transplant, which may play an essential role in the expression of intimacy, such as a kiss from the lips of a facial graft or a caress with the hands of an upper extremity transplant.254 Assessments of social support in the process of screening candidates need to assess not merely the level of general

248Chang and Mathes, 556–557; Amer et al., Pomahac, Gobble and Schneeberger, 11; Kumnig, Jowsey and DiMtrini, 191; Breidenbach et al., 1043–1044; Klapheke et al., 456.
249Murphy, Zuker and Borschel, 1450.
250Kay Toombs, cited in Freeman and Jaoude, 79.
251Kiwanuka et al., 1558–1563; Shanmugarajah, Hettiaratchy, and Butler, 295; Evans, 154; Siemionow, Gharb and Rampazzo, 636; Bueno, Diaz-Siso and Pomahac, 1576; Edwards and Mathes, 117; Alexander et al., 62; Agich and Siemionow, 707–708.
252Yi and Guo, 178; Infante-Cossio et al., e269.
support but also the capacity of those in the support system to accept the graft and interact with the patient and graft after engraftment.

2.5.2.3 Patient Selection

Patient screening and selection is widely regarded as critical to the success of VCA. Candidates must qualify in terms of the extent of the defect and the degree to which it is amenable to transplant, as well as on the basis of psychological stability, appropriate motivation, cognitive function, compliance history, attitude toward risk and social support. Jaimie T. Shores gives a very thorough description of the screening for hand transplant candidates at the Johns Hopkins University School of Medicine program. He begins with the initial contact from the patient, describes the initial visit and subsequent screening visit, lists screening test panels and consultations, and describes the psychiatric, psychological and social screening. Chad R. Gordon et al., outline their “FACES” tool for selecting face transplant candidates at the Cleveland Clinic, offering both inclusion and exclusion criteria. Various methods are used at different institutions to determine whether or not candidates are qualified, in part due to limited research into which factors are good predictors of outcome. In 2014, the Chauvet Workgroup, composed of specialists in surgery, medicine, psychiatry, psychology, social work and ethics, was formed to address the question of what factors should be considered in screening and what weight should be given to various factors in light of outcomes thus far.

Up to this time, screening and evaluation have eliminated a large percentage of interested candidates. Chang and Mathes report that the Louisville program interviewed 213 candidates and approved only nine, while an Italian program approved

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256 Edwards and Mathes, 114–115; Klapheke et al., 453–457; Breidenbach et al., 1041; 1046; Chang and Mathes, 558; Samuel Taylor-Alexander, “On Face Transplantation,” Anthropology Today 29, no. 1 (2013): 13–16; Shores, Imbriglia and Lee, 1865; Renshaw et al., 865; Losee, Fletcher and Gorantla, 261–263; Wo, Bueno and Pomahac, 617.


259 Kumnig, Jowsey and DiMartini, 190.; Gordon et al., 312.

260 Jowsey-Gregoire et al.
only four out of more than five hundred.\textsuperscript{261} Psychosocial characteristics sought in candidates include assertiveness, excellent social support, a strong sense of self, optimism, self-awareness and conscientiousness.\textsuperscript{262} Physical characteristics sought include the absence of chronic infections, active cancers, serious coronary artery disease and various metabolic diseases.\textsuperscript{263} In upper extremity VCA, tissue loss through sharp amputations are preferred to those from crush injuries, and more distal amputations are preferred to more proximal ones.\textsuperscript{264} In face transplantation especially, it is appropriate to also assess the patient for sufficient reconstructive options in the event of graft failure.\textsuperscript{265}

Patients are selected very carefully for a number of reasons. First, the surgery and subsequent rehabilitation are demanding and the failure to adhere to the physiotherapeutic or immunosuppressant regimens will result in very poor outcomes, including failures in which grafts will need to be removed.\textsuperscript{266} Second, donor tissues seldom become available, represent a significant sacrifice on the part of donor families, and thus should be allocated only to recipients who give strong evidence that they will honor the sacrifice of the donor family through effort and adherence.\textsuperscript{267} Finally, in a relatively new area of research, early failures can do great harm to the prospects of the field.\textsuperscript{268}

\subsection*{2.5.2.4 Psychological Consequences of Graft Loss}

VCA patients are always susceptible to graft loss, due to chronic rejection, infection or other causes. Thus far, there has been only one total graft loss and one partial graft loss in facial transplantation, though there have been several total losses in upper extremity transplantation.\textsuperscript{269} It has even been recommended, with regard to upper extremity transplants, that prospective patients be advised of the “possibility in the long run of chronic rejection of hands that would be theirs only

\textsuperscript{261}Chang and Mathes, 557.

\textsuperscript{262}Furr et al., 563; Coffman and Siemionow, “Psychological Outcomes,” 374; Pushpakumar et al., 954; Lantieri, 251; Tintle et al., “Hand Transplantation,” 2; Hautz et al., “How Reconstructive Transplantation is Different,” 3505. For psychological contraindications, see Coffman and Siemionow, “Ethics of Facial Transplantation Revisited,” Psychosomatics 54, no. 4 (2013): 185; Lantieri, 251; N. Roche et al., “Long-term multifunctional outcome and risks of face vascularized composite allotransplantation,” 2045.

\textsuperscript{263}Losee, Fletcher and Gorantla, 260–261; Shores, 541–542.

\textsuperscript{264}MacKay, Nacke and Posner, 77.

\textsuperscript{265}Coffman and Siemionow, “Psychological Outcomes,” 374; Vercler, 379–380.

\textsuperscript{266}Edwards and Mathes, 115; Bueno, Diaz-Siso and Pomahac, 1575; Evans, 153; Shanmugarajah, Hettiaratchy and Butler, 296; Salminger et al., 4.

\textsuperscript{267}Bueno et al., 256; Weissenbacher et al., 641.

\textsuperscript{268}Shores, 539; Siemionow, Gharb and Rampazzo, 638; Dean and Talbot.

\textsuperscript{269}Siemionow, Gharb and Rampazzo, 633–639; Pomahac, Gobble and Schneeberger, 11; Siemionow and Ozturk, 254; Clarke and Butler, 1097; Tintle et al., “Hand Transplantation,” 5; E. Morelon et al., “Face Transplantation: Partial Graft Loss of the First Case Ten Years Later”.

\textsuperscript{46}2 Vascularized Composite Allotransplantation
temporarily”. While loss of upper extremities would certainly have negative psychological effects upon the patient, these would be somewhat mitigated by the relatively straightforward reconstructive options and the existence of a return to prostheses use as an option. The loss of a facial graft, however, would likely have a far more profound psychological impact. Loss of the graft would return patients to a state of disfigurement and functional limitations equal to or greater than that experience after the original trauma or at the worst point of the disease process that led them to seek out the surgery. Reconstruction after the loss of a facial graft, if possible, would be difficult, requiring multiple surgeries. Psychological impact after facial graft loss would also tend to be greater than that after upper extremity graft loss because the face plays a much larger role in one’s sense of identity and in the manner one presents one’s self to the world.

2.5.3 Procurement and Allocation Concerns

In both Europe and the United States, regulations for the procurement and allocation of organs differ from those regarding tissues. As noted earlier, this has influenced the transition in name for the field from composite tissue allotransplantation to vascularized composite allotransplantation. In the United States, VCAs have been redefined as organs and the process is underway to develop regulations for procurement and allocation under the oversight of the Organ Procurement and Transplantation Network. VCA grafts are also treated as organs by law in France.

Because the retrieval of upper extremity and facial grafts is much more disfiguring for donors than the retrieval of solid organs, it is anticipated that the strict enforcement of first person consent rules as they apply to solid organs will not be appropriate for these new grafts. There is concern that a procurement approach which is too aggressive might decrease overall organ donation levels. The small

270 Dumont, Sann and Gazarian, 148.
271 Zor, 161.
272 Lantieri et al., 376; Siemionow and Ozturk, 257; Edwards and Mathes, 119.
274 Schneeberger, Morelon and Landin, 1088–1089.
275 See note 38.
276 McDiarmid, 665–666. The recognition of VCA grafts as organs was recommended by many, including Cendales, Rahmel and Pruett, 1086.
277 Cendales, Rahmel and Pruett, 1086.
278 McDiarmid, 667–668; Lantieri et al., 375.
279 Chong and Pruett, 1371.
number of approved candidates for facial and upper extremity VCAs at this time has made the development of regional or national allocation systems impractical, but if the scale of VCA were to increase greatly, such systems would become workable and valuable.280

Another concern related to procurement is the necessarily disfiguring effect of graft recovery. While both facial and upper extremity graft recovery is disfiguring for the donor, the recovery of facial grafts is far more disfiguring. In facial VCA, some attempt to restore the donor face for viewing by next-of-kin or simply out of respect for the dignity of the donor has become standard. In some countries it is even a legal requirement.281 Most attempts to restore donor faces have consisted of the creation of a mask by fairly traditional means, using acrylic resins or silicone and the skills of a maxillofacial prosthetics technician or an anaplastologist to match skin color. New methods involving digital imaging and 3-D printing are being explored and are likely to play a larger role in the future.282

### 2.5.4 Financial Costs

The financial cost associated with facial and upper extremity VCAs is substantial, though it has received little attention in the literature.283 A full accounting must consider not only the costs of the surgery itself but also the costs involved in screening both accepted and rejected candidates, costs incurred in procurement of the graft, the costs of post-surgical therapy which may last for years, lost work, the cost of immunosuppressants for the remainder of the patient’s life unless the graft is removed, and the cost of treating the side effects of immunosuppression, such as diabetes and hypertension.284 Success in the effort to induce tolerance could have a major effect on costs, since the cost of immunosuppressants is estimated to be over half the total.285

280Kiwanuka et al., 1566; Weissenbacher et al., 641; Evans, 152; Cendales, Rahmel and Pruett, 1087.
282Grant et al., 720–724. Galvez et al., 343, report the use of 3-D modeling and printing for replacing the limbs of the pediatric donor of hands in a surgery which took place in 2015.
285Chung et al., 593.
Chung et al., estimated the lifetime costs of a single hand transplant to be $528,293 and the cost of a bilateral transplant to be $529,315. This may be compared to costs for treatment by means of prostheses at $20,653 and $41,305. Siemionow, Gharb and Rampazzo offer a much lower figure for the cost of facial transplantation, though it is not clear whether their accounting includes everything that Chung et al., included in their accounting of the costs of upper extremity transplants. Siemionow, Gharb and Rampazzo do note a differential in cost for face transplants between the United States and Europe, with European costs being roughly seventy-nine percent of U.S. costs.

Some attempt has been made to evaluate the value of facial and upper extremity VCA in terms of expense per quality-adjusted life years (QALYs). However, given that the economic costs remain uncertain, these attempts are subject to criticism. The evaluations are also subject to criticism because the quality of life measure was based on estimates by a survey of medical students who were not representative of the general population, and certainly not of the persons bearing defects which would make them potential candidates for VCA. More focused work on assessing the effect of VCA on quality of life is needed.

Currently the financial costs of VCA are not imposed on the patient or the patient’s insurance. Institutions performing the procedure have carried the cost, aided by research grants and other sources of income. Should facial or upper extremity transplant programs continue, there is a concern over whether insurance companies or government health care systems will be willing to bear the expense. Indications thus far have been that this is unlikely. A recent attempt to get a hand transplant covered in Switzerland was denied by a Swiss health technology assessment. If insurance companies or governments do not bear the cost, facial and upper extremity VCA would almost certainly continue to be rare.

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287 Siemionow, Gharb and Rampazzo, 636.

288 Chang and Mathes, 557–558; Tintle et al., “Hand Transplantation,” 7; Shores, Imbriglia and Lee, 1865; Errico, Metcalfe and Platt; Edwards and Mathes, 121.


290 Edwards and Mathes, 121; Shores, Imbriglia and Lee, 1865.

291 Edwards and Mathes, 121; Errico, Metcalfe and Platt; Shores, Imbriglia and Lee, 1865; Tintle et al., “Hand Transplantation,” 6–7; Siemionow and Ozturk, 257; Coffman and Siemionow, 186.

2.5.5 Ethical Issues

There is a growing body of literature focusing on the ethics of facial and upper extremity VCAs, including in recent years some featuring a broad discussion of multiple ethical issues\(^\text{293}\) and one article by Kiwanuka et al., examining the history of the ethical debate in facial transplantation.\(^\text{294}\) A large number of other articles focus on one or two ethical features of VCA, typically discussing either upper extremity or facial VCA, but seldom both.

In 2008, Chung et al., undertook a review of ethical principles in plastic surgery literature, which included a number of articles concerning face transplantation. While the scope of their review did not extend to bioethics journals,\(^\text{295}\) what they discovered regarding the treatment of ethics in facial transplantation is intriguing. In all, they found less than one percent of all the plastic surgery literature was composed of articles clearly focused on ethics. Of a mere 110 articles they found, twenty dealt with ethics in facial transplantation specifically. Chung et al., then identified major and minor themes in these articles according to the four principles of Beauchamp and Childress. Of interest is that in all 110 articles, they identified respect for autonomy as the most common major theme, appearing more than twice as often as any other; however, when only the articles concerned with face transplantation are considered, beneficence and non-maleficence together appear as the major theme more than twice as often as respect for autonomy. Also of interest is that the principle of justice appears only once in the facial VCA ethical literature they review, and then only as a minor theme.\(^\text{296}\) The account of the evolution of the ethical debate by Kiwanuka et al., also involved a literature review of 110 articles and analyzed them by theme, though not using the four principles of Beauchamp and Childress as their guide. Nonetheless, interpretation of their analysis would suggest a similar distribution with regard to emphasis: beneficence and non-maleficence first, then respect for autonomy and finally justice.\(^\text{297}\)

What follows is an exploration of ethical themes in relation to facial and upper extremity VCA. This exploration will consider the four principles of respect for autonomy, beneficence, non-maleficence and justice, as well as two additional principles, vulnerability and dignity. As noted above, the practical concerns in VCA are deeply intertwined with the ethical concerns, and this will be demonstrated below.

\(^\text{293}\)Kalliainen; Edwards and Mathes; Errico, Metcalf and Platt; Chang and Mathes; Coffman and Siemionow, Wiggins et al., Johnson and Corsten; Doumit et al.

\(^\text{294}\)Kiwanuka et al., \textit{passim}.

\(^\text{295}\)The author of this dissertation was able to identify fourteen additional articles addressing the ethics of VCA within the time frame surveyed by Chung et al., and twenty-seven more since. Time constraints prevented the analysis of these articles according to bioethical themes. The article by Toure et al., shows that discussion of VCA in bioethics journals was quite robust as of 2006; 790.


\(^\text{297}\)Kiwanuka et al., 1559–1565.
2.5.5.1 Justice

In bioethics, the principle of justice is primarily concerned with distributive justice, or “fair, equitable and appropriate distribution”\(^\text{298}\) of scarce goods and services. With regard to facial and upper extremity VCA, this would be related to patient selection, to the allocation of upper extremity and facial donations, and to discussions of the expense of the treatment, including cost/benefit determination. Indeed, there has been considerable debate around these issues.

At this point, since no formal procedure for allocation of upper extremity or facial tissue donations has been implemented, allocation takes place at the level of the medical center and is essentially the same as patient selection and matching when a graft becomes available.\(^\text{299}\) A synopsis of the debate may be derived from reading the earlier sections on patient selection and on procurement and allocation. At the core of this aspect of justice in VCA is the idea that it is fair, equitable and appropriate to allocate the donor tissue to those who have a clear, compelling need and who are deemed most likely to maintain the graft through psychological acceptance and adherence to immunosuppression and to maximize the functionality through consistent participation in physiotherapy.\(^\text{300}\)

The second major aspect of justice discussed in the bioethics literature concerns the costs in light of limited resources for health care overall. VCA may be technically feasible and yet not be a just use of scarce resources. Discussions of the economic dimensions of VCA and cost/benefit analyses, including the use of QALYs, appear in several articles.\(^\text{301}\) Evans reports that this aspect of justice is a concern expressed by some members of VCA medical teams.\(^\text{302}\) The article by Chung et al., is devoted solely to an economic analysis of hand transplantation, but its conclusions have been questioned.\(^\text{303}\)

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300Agich and Siemionow, 708–709; Barker et al., “Research and Events,” 241; Losee, Fletcher and Gorantla, 260–264; Vercler, 80; Siemionow and Gordon, 1232–1235; Siemionow, “Ethical Considerations,” 157–159; Cendales, Rahmel and Pruet, 1086; Coffman and Siemionow, 185–186; Shores, Imbriglia and Lee, 1865–1866; Freeman and Jaoude, 80; Lantieri, 252. Dean and Talbot have made the interesting argument that nonadherence among the early VCA recipients may have been a consequence of the “risk-tolerant innovator” personality style which led these persons to pursue the treatment in the first place.
301Tintle et al., “Hand Transplantation,” 6–7; Siemionow, Gharb and Rampazzo, 636–637; Lantieri, 252; Shores, Imbriglia and Lee, 1865; Kallianen, 549; Chang and Mathes, 557–558; Errico, Metcalfe and Platt, 3; Edwards and Mathes, 120–121; Coffman and Siemionow, 186; Freeman and Jaoude, 80; Kiwanuka et al., 1565.
Early in 2015, research appeared claiming that a QALY calculation, based on survey results from a small number of unilateral amputees, showed that there was no preference toward hand transplantation given the current risk profile.\(^{304}\) Yet with the small sample and the failure to include bilateral amputees, this study does not present an especially strong case against upper extremity VCA. Further research is needed to resolve the uncertainty over costs and benefits, and progress in the field of VCA or in the field of prosthetics may alter the balance significantly.\(^{305}\)

With regard to facial VCA, the difference in cost between VCA and conventional treatments is less extreme. Conventional face reconstruction for persons with major tissue deficits involves a series of operations over the course of many months or even years. The cumulative cost can be comparable to the costs associated with facial VCA, and the outcome far less satisfactory both cosmetically and functionally. Furthermore, as experience is gained, the cost of VCA is likely to come down, as has been the case with other new procedures, including forms of solid organ transplantation.\(^{306}\)

### 2.5.5.2 Beneficence and Non-maleficence

As Chung et al., observed in their review of plastic surgery literature concerned with ethics, the themes of beneficence and non-maleficence have a tendency to appear together.\(^{307}\) Beneficence refers to the duty of those in health care to act in ways that lead to benefits for the patient.\(^{308}\) Non-maleficence may be described as the “obligation not to inflict harm on others”.\(^{309}\) Clearly, both principles may be applied to the evaluation of a single act.

The ethical debate regarding facial and upper extremity VCA up to this point has been dominated by the consideration of these two ethical themes.\(^{310}\) Risk/benefit analyses, which are efforts to determine whether the good accomplished outweighs the burdens (harms) and risks imposed, are routine in articles on VCA, even those

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\(^{307}\) Chung et al., “Systematic Review,” 1714.

\(^{308}\) Beauchamp and Childress, 197–199.

\(^{309}\) Beauchamp and Childress, 149.

\(^{310}\) See notes 222 and 223.
that are not primarily focused on ethics.\textsuperscript{311} In the review of 110 articles by Kiwanuka et al., they claim that risks and benefits are discussed explicitly in 64.5\% of the articles. However, an evaluation of the other “core issues” they found suggests that several of them are concerned with risk/benefit analysis even if they do not use that language. For example, articles that discuss immunosuppression, transplant failure, quality of life, the importance of the face, or that disfigured people cannot live normal lives, address key concerns in the risk/benefit analysis.\textsuperscript{312}

For our purposes, the consideration of burdens, risks and benefits in regard to the ethical principles of beneficence and non-maleficence will draw on a number of specific issues raised in the literature: patient selection, immunosuppression and its side effects, psychological and identity concerns, program quality, privacy concerns, and harm to donors. Each of these is a factor in determining whether VCA can be justified in light of the ethical obligations to benefit patients and to refrain from doing harm.

Patient selection, as we have seen, is also relevant to the ethical principle of justice, inasmuch as it is concerned with allocating the graft and the institutional resources to patients in a way that is appropriate and fair. It is relevant to the ethical principles of beneficence and non-maleficence because patients subjected to the burdens and risks of the surgery and subsequent immunosuppression and therapy must be those who are reasonably expected to benefit. In part, this means that an effort should be made to assure that they have the psychological and social resources to persist in the physiotherapy, psychotherapy and immunosuppression required to maximize the function and longevity of the graft.\textsuperscript{313}

The first hand transplant may have failed because insufficient attention was given to the recipient’s psychological condition. Dickenson and Widdershoven note that he had previously rejected his replanted arm, denying that it was “really his,” and later ceased adhering to his immunosuppression regime when he came to feel the same way about his allograft.\textsuperscript{314} Post-transplant psychiatric disorders are not infrequent in upper extremity recipients, often leading to non-adherence with physiotherapy, immunosuppression or both. In some cases, the non-adherence has led to graft loss.\textsuperscript{315}

\textsuperscript{311}A more accurate term would be burdens and risks versus benefits, since patients face both certain burdens and merely probable risks in their pursuit of benefits. Since this way of expressing the calculations involved in determining the ethical justification is not yet widely used, we will continue to employ the traditional term, risk/benefit.

\textsuperscript{312}Kiwanuka et al., 1561.

\textsuperscript{313}Tintle et al., “Hand Transplantation,” 2; Chang and Mathes, 556–557; Losee, Fletcher and Gorantla, 261–263; Renshaw et al., 865; Agich, 133–134.

\textsuperscript{314}Dickenson and Widdershoven, 116.

\textsuperscript{315}Tintle et al., “Hand Transplantation,” 5; Errico, Metcalfe and Platt, Kumnig and Jowsey-Gregoire, 94; Jowsey-Gregoire et al. According to Siemionow and Ozturk, 257, multiple losses of upper extremity grafts in China were the result of lack of immunosuppression, but the fault may not have been the patients’, as it was only provided for a short time by the authorities.
The risks and harms associated with immunosuppression are perhaps the most discussed issue in connection with beneficence and non-maleficence in VCA. The risks include greater susceptibility to opportunistic infections, metabolic disturbances that may lead to co-morbidities such as renal failure or post-transplant development of diabetes, an increased risk of malignancies, cardiovascular problems and the possibility that patient longevity will be decreased by the treatment. These are obviously substantial risks, and require a high likelihood of substantial benefits in order for VCA to be ethically justified.

The arguments which claim the benefits are indeed substantial frequently note that facial and upper extremity VCA offers both functional and cosmetic benefits. Successful upper extremity transplants not only provide more natural-looking limbs but also limbs which, after therapy, can be superior to prostheses in their function. Facial transplant recipients, as stated above, may obtain restoration of olfaction, and the ability to eat, breathe and communicate more naturally. In addition, as Agich points out, without facial transplantation, patients face the alternative of “multiple burdensome reconstructive procedures and a life of social isolation”.

Psychological effects and consequences for patient identity also figure prominently in discussions of the risk/benefit ratio. Early on, concern over identity transfer in facial transplantation was common. This has subsided with clinical experience showing that recipients do not resemble the donors to a significant degree. The inability of upper extremity transplant patients to identify with the graft was also discussed as a risk, particularly in light of the failure of the first hand transplant patient to do so. For upper extremity patients since, this does not seem to have been a major problem.

In reply to those who have argued that the psychological risks of transplant were too high, several have replied that the psychological suffering associated with disfigurement must also be considered. In fact, psychological follow-up of facial transplant recipients have shown improvement in anxiety and depression levels and increases in the perception of quality of life. Chang and Mathes, assert that upper

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316See note 146.
318Lengele, 508; Losee, Fletcher and Gorantla, 260; Edgar, 126; 129; Pomahac, Gobble and Schneeberger, 5–6; Kalliainen, 549.
319Agich, 136.
320Kiwanuka et al., 1559.
321Kiwanuka et al., 1565; Coffman and Siemionow, “Ethics Revisited,” 184; Kalliainen, 549–550; Wiggins et al., 5; Errico, Metcalfe and Platt; Agich, 133–134; O’Neill and Godden, 444; Swindell, 449–452; Evans, “Historical Overview,” 154; Agich and Siemionow, 25–27; Alexander et al., 61; Losee, Fletcher and Gorantla, 260; Hurlburt, RA148.
extremity transplantation has improved patients’ body image. Furr et al., provide a thorough description of the psychological implications of disfigurement, noting that facial disfigurement in particular tends to become “a master status and leads to prejudice and discrimination, stereotyping and, frequently, social isolation”. Paradis et al., give an excellent description of how the functional impediments of disfigurement could have a troubling psychological impact.

Program quality is given attention in a number of articles. The connection between program quality and the principles of beneficence and non-maleficence is that unless transplant programs are of sufficient quality, they may expose patients to excessive and unnecessary risks. The need for sufficient program quality was first advanced as part of the justification for VCA by the University of Louisville team as it began developing its program. Elements of program quality include the skill and experience of the team, the ethical climate of the institution and public and professional discussion and evaluation. Agich, in commenting on the Louisville approach, emphasizes that the skill of the team must refer to all members of the team, not just those directly involved in the surgical procedures. The research of Zhu et al., which looked at failure rates in facial VCA, lends some support for the claim that program quality is essential to the success, and thus the ethical justification, of VCA.

Privacy and confidentiality concerns also raise the issue of potential harm to recipients, donors and their families, and thus must be considered under the principle of non-maleficence. Concern for confidentiality in bioethics reaches back to its earliest days, where it is a component of the Hippocratic Oath. It also appears in the first code of ethics published by the American Medical Association in 1847, and continues to appear in contemporary codes such as the Declaration of Geneva. However, the privacy of upper extremity and facial graft recipients has proven almost impossible to fully protect.

Upper extremity and facial VCA procedures have elicited intense media interest, which was anticipated. Despite efforts to keep information about the recipient and donor of the first facial transplant private, the names of both the recipient and donor

323Chang and Mathes, 555.
324Furr et al., 560–564. See also Johnson and Corsten, 276; and Edgar, 130.
325Paradis et al., 896–897.
326Kalliainen, 551.
328Agich, 132–133.
quickly appeared in the press. Given the level of public interest, a number of considerations must be taken in VCA with regard to patient privacy and confidentiality. First, patient selection must consider the likelihood of the patient’s identity and images being exposed. As Furr et al., put it, candidates “must be persons of sufficient confidence and composure to withstand the attention”. Second, informed consent and patient education before surgery should address the high probability that the recipient will be the subject of widespread media attention. Third, care should be taken to prepare the transplant team, ancillary services and others in the institution for the task of dealing with the media onslaught and for protecting the privacy of the recipient, the donor and their families to the highest degree possible.

Protecting privacy can be challenging not only due to the curiosity of the media but also because publicity may have perceived benefits to the institutions and the staff involved in performing these revolutionary procedures. Evans, in her description of health care team members involved in a facial transplant, says they were aware that the procedure generated “good will and good press” for the institution. Even so, she states, they were conscious of the risk to patient privacy and felt the attention was “intrusive”. Samuel Taylor-Alexander expresses concern for both privacy and patient well-being by raising the issue of nationalism and national pride as motives driving the development of some VCA programs.

Special concern over the potential harm to pediatric patients has been discussed by Doumit et al., in response to the announcement that Boston Children’s Hospital has established the first pediatric hand transplantation program. Doumit and colleagues were concerned about the inclusion of pediatric patients on several grounds. They noted that children are at higher risk for post-transplant malignancies, and that VCA in children will likely be complicated by the effects of immunosuppression on growth of the graft while increasing the risk of fractures. They also envisioned problems with rejection and graft loss due to the well-established propensity of

333 Furr et al., 563.
334 Agich and Sieminow, 708–709; Paradis et al., 898; Lamparello et al., 285.
335 Agich, 135; Coffman and Siemionow, 183.
adolescents to struggle with adherence to the immunosuppressive regimen in solid organ transplantation. Similar non-adherence in the physiotherapy regimen required in upper extremity VCA would severely limit the functional success of grafts. As it happened, the first pediatric hand transplant requiring immunosuppression took place in 2015 and was performed on an 8-year-old child who was already receiving immunosuppression as a result of an earlier kidney transplant.340

The final topic of relevance to non-maleficence is concern for donors and donor families in VCA. The recipient and his or her family are a primary focus of concern, but donors and their families can also be wronged and harmed.341 This may have implications for donor consent, and some have questioned whether consent for facial donation should ever be allowed solely on the basis of substituted judgment, or whether it should always require first person consent as well.342 Concern about possible psychological harm to donor families has also contributed to the standard practice of some form of cosmetic restoration for donors after graft retrieval.343

2.5.5.3 Autonomy

The term autonomy was coined by the ancient Greeks as a way of describing certain city-states and distinguishing them from other cities or regions. An autonomous city-state was one that was self-governing. This political meaning of “autonomy” remained the primary meaning until the eighteenth century.344 In that century, Immanuel Kant used the term in his moral philosophy. Drawing in part on the works of Jean-Jacques Rousseau,345 Kant set out to establish a moral philosophy.

341 Siemionow and Ozturk, 256.
342 Freeman and Jaoude, 80.
343 Lantieri, 252; Edwards and Mathes, 117.
344 Beauchamp and Childress, 103–104.
grounded solely in reason. For Kant, autonomy of the will referred to the capacity of the will to be moved by reason alone, and not by other forces, either from within the person or from outside the person. 346

As shall be shown in a subsequent chapter of this book, Kant’s notion of autonomy is influential upon but not identical with the concept of autonomy in contemporary health care ethics. Beauchamp and Childress, who have done the most to promote the concept of respect for autonomy as one of the pillars of bioethics, acknowledge their debt to both Kant and to nineteenth century philosopher John Stuart Mill and his notion of liberty. Drawing on these sources, Beauchamp and Childress contend that respect for autonomy implies that persons with decisional capacity ought to be provided with sufficient information so that they may choose for themselves which treatments they do or do not want. 347

In the United States, where the writings of Beauchamp and Childress are most influential, autonomy serves almost exclusively as a justification for informed consent. In Europe, however, the role of autonomy is broader. Jacob Dahl Rentdorff, in his review of basic ethical principles in European bioethics and biolaw, offers five “important meanings of autonomy.” Rentdorff, quoting Paul Ricouer, asserts that the European understanding of autonomy “is based on the vision of ‘the good life for and with the other in just institutions’. 348

The VCA literature that addresses ethics tends to adhere to the understanding of autonomy associated with Beauchamp and Childress, discussing autonomy only in terms of informed consent. 349 Some express concern that the desperation of potential candidates may undermine their capacity to give consent. 350 The findings of Barker et al., that people are willing to accept more risk for a face transplant than for several other kinds of transplants could be taken as evidence of this desperation. 351 Others argue, however, that a blanket disqualification smacks of paternalism. 352 Kalliainen draws parallels between the interests of VCA candidates in therapy that bears significant risks and the interests of people infected with HIV in

347Beauchamp and Childress, 103–104.
349Kalliainen, 548; Johnsen and Corsten, 275; Coffman and Siemionow, 182–183; Chang and Mathes, 555.
350Huxtable and Woodley, 510–513; Strong, 13. Dickenson and Widdershoven, 117–118, provide a notable exception, giving a more European approach in their interpretive and deliberative models of the doctor-patient relationship.
352Hurlburt, RA149; Chang and Mathes, 556; Johnsen and Corsten, 275–277; Katrina A. Bramstedt, “Informed Consent for Facial Transplantation,” in The Know-How of Face Transplantation, Maria Siemionow, ed. (New York: Springer, 2011), 255; Agich, 134; Freeman and Jaoude, 78.
the early 1990s who some felt at the time should not be exposed to the risks of largely untried experimental therapies. In addition, VCA advocates note that vulnerability and distress are characteristic of many people who are asked for consent in the medical setting. Proponents of facial and upper extremity VCA contend that those who might not be able to rationally weigh the burdens, risks and benefits of the proposed treatment would be identified in the process of screening, and that it would be unethical to make the treatment unavailable to others who would be capable of giving voluntary consent.

A second objection to the possibility of informed consent in VCA is based on the extremely limited information available. Consent cannot be informed, it is argued, when so little information is available. The counterargument given is that sufficient information is available from animal studies, human solid organ transplants and limb replantation. However, Agich and Renshaw et al., do argue that special attention must be given in VCA to assessing patient understanding of the information offered. Furthermore, VCA advocates contend, to demand more information than is available for VCA is unreasonable, and such a high standard would have a chilling effect on a great deal of beneficial medical research. In the words of Hurlburt, “Following [this] line of reasoning, it may be the case that all new forms of surgery... may be such that informed consent cannot be obtained”. As in all research, it is assumed that there is information not yet known, and this fact can and should be revealed to candidates.

2.5.5.4 Dignity

Having addressed the standard quartet of bioethical principles explicated in multiple editions of Beauchamp and Childress’ *Principles of Biomedical Ethics*, one could

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353 Kalliainen, 548.
354 Kalliainen, 548.
355 Chang and Mathes, 558; Barker et al., “Ethical Considerations,” 106; Renshaw et al., 863–864.
357 Agich, 134; Renshaw et al., 866. Paradis et al., offer an extended description of the informed consent process for the first face transplant in the United States, 898–899.
358 Shores, Imbriglia and Lee, 1863; Siegler, 2779–2782; Barker et al., “Research and Events,” 243; Morris et al., 119; Barker et al., “Ethical Considerations,” 108; Siemionow and Gordon, 1234; Clarke and Butler, 1091; Hurlburt, RA149–RA150; Alexander et al., 62; Pomahac et al., 1696.
359 Hurlburt, RA149.
360 Edwards and Mathes, 116.
argue that we have treated the topic of ethics in relation to VCA sufficiently. After all, principlism is the dominant approach to bioethics and Beauchamp and Childress are its leading purveyors. Yet there are both other approaches and other principles worth considering. Of special value in the consideration VCA, given its high stakes for patients and its still-experimental status, are the principles of respect for human dignity and human vulnerability. Dignity and vulnerability are ethical principles more commonly associated with bioethics outside the United States. Our discussion will treat dignity first, while vulnerability will be examined in the next section.

The appropriateness and usefulness of dignity as a principle has been the subject of much dispute. Wolfhart Pannenberg asserts that dignity is something “that none of us has by merit, that none of us can receive from others, and that no one can take from us”. At the heart of the idea of human dignity, according to Ronald Dworkin, is the supposition that “there are ways of treating a [human being] that are inconsistent with recognizing him as a full member of the human community, and… that such treatment is profoundly unjust”.

Some give dignity the leading role in bioethics. Others, however, have argued that the understanding of dignity is insufficiently precise, while yet others have argued that its functions are already accounted for in other principles. It is also considered suspect by some because of its historical association with religion and

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its present popularity with those who tend to be conservative in their ethics. \(^{367}\) In
fairness, it may be noted that the principles of respect for autonomy and justice are
also subject to criticism on theoretical, cultural and political grounds.\(^ {368}\) Furthermore, the criticisms of dignity as a principle in bioethics have been ably
answered by a number of authors who, while admitting that the use of dignity in
bioethics can at times exhibit these flaws, assert that the principle of dignity is
capable of better when properly understood. \(^ {369}\) Rentdorff gives a particularly robust
definition of dignity as it should be used in bioethics.\(^ {370}\)

The term has its origins in ancient Rome among the Stoics. Leget notes that
dignity had two meanings for Cicero. \(^ {371}\) The first referred to public recognition of
the special status of particular persons. A recognition of dignity called for behaviors
that demonstrated respect for the status. For example, gestures of deference might
be made by one of inferior status. Yet the bearer of the status was also expected to
behave in certain ways consistent with the dignity he or she happened to bear, i.e.,
to behave in a dignified manner. \(^ {372}\)

The second meaning for Cicero was “the intrinsic and characteristic quality by
which humans are distinct from other beings.” \(^ {373}\) To put it another way, Cicero
universalized the concept of dignity, claiming that all humans held a special status
in comparison to other things in the world (animals, plants, etc.), and that this
special status both deserved recognition from other humans and imposed special
expectations upon all persons to act in ways which were appropriate to their
inherent dignity. \(^ {374}\)

\(^{367}\) Ashcroft, 680, claims that Kass “asserts that traditional morality is coherent with what dignity
requires.” Sulmasy notes the predominance of dignity in the vocabulary of Church after the second
Vatican Council, claiming that, “in Gaudium et Spes, almost every other word is ‘dignity’ [and]
the decree on religious freedom is entitled Dignitas Humanae.” Daniel P. Sulmasy, “Death with
Dignity: What Does It Mean?” Josephinium Journal of Theology 4, no. 1 (1997): 18; Cochrane,
236–237; Immaculada De Melo-Martin, “An Undignified Bioethics: There is No Method in this

\(^{368}\) There are profound tensions between those who approach autonomy from a Kantian perspective
and those whose interpretation leans more toward Mill and negative liberty. As for justice, the
point of view taken by Robert Nozick and associates is at odds with that taken by Rawls and
others.

\(^{369}\) De mello-Martin, passim; Andorno, “Dual Role,” passim; Carlo Leget, “Analyzing Dignity: A
Perspective from the Ethics of Care,” Medicine, Health Care and Ethics 16 (2013): 945–952;
Sulmasy, passim; Foster; Edlund, M., L. Lindwall, I.V. Post, and U.A. Lindstrom, “Concept

\(^{370}\) Rentdorff, 237.

\(^{371}\) Leget, 946. See also Roberto Andorno, “Human Dignity and Human Rights,” in H.A.M.J. ten

\(^{372}\) John Kleinig and Nicholas G. Evans, “Human Flourishing, Human Dignity and Human

\(^{373}\) Leget, 946.

\(^{374}\) Kleinig and Evans, 548–552.
Stoic thought was influential in post-Constantinian Christian thought, which linked the idea of dignity to the teaching that humans are made in the image of God. The notion was further developed in the Renaissance by Gianozzo Manetti and Giovanni Pico della Mirandola, who saw the capacity of humans to pursue transformation as the basis of dignity. Dignity was later explored by Kant, who linked it to autonomy, calling autonomy the basis of dignity. According to Kant, all things have either “a price or a dignity.” Things with a price can be replaced by an equivalent, while things having dignity have no true equivalent and are irreplaceable.

In more modern times, as van der Graaf and van Delden note, a link has been forged between unconditional dignity and human rights. Particularly after the Second World War, this emphasis is strengthened. Others have linked dignity to human flourishing, personhood and vulnerability.

Much of the current debate about dignity and its appropriateness in bioethical debate is due to the fact that the idea of dignity remains fluid, if not amorphous. One scholar calls it, “intangible, yet luminous …a vague though powerful concept”. The concept becomes considerably less vague when clarified by sorting out different uses or versions. Andorno observes that dignity plays very different roles in bioethics in relation to policy formation and patient care. In the former case, it is more general and better grasped by descriptions of what it forbids rather than by descriptions of what it allows or encourages. In the latter case, it calls for close attention to the vulnerabilities of a particular patient in a specific setting.

Daniel Sulmasy speaks of “varieties of human dignity,” distinguishing three: intrinsic, attributed and in florescent. Intrinsic dignity refers to that “worth, stature or value human beings have simply because they are human”; attributed dignity is that conferred upon one by one or more others; and in florescent dignity refers to the dignity attached to a manner of living that reflects or leads to human flourishing. Leget offers another tripartite description, with the terms subjective dignity, social and relational dignity and intrinsic dignity. Leget’s intrinsic dignity is similar to Sulmasy’s variety of the same name. Subjective dignity refers to an individual’s sense of worth or honor, which may or may not be grounded in objective reality.

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375 Leget, 946; Andorno, “Human Dignity,” 46–47.
376 Kleinig and Evans, 551.
378 Kleinig and Evans, 553.
382 Andorno, “Dual Role,” passim.
Social and relational dignity is that sense of dignity conferred by the actions and expressions of others.  

Lennart Nordenfelt’s description of four kinds of dignity has also been influential. He calls inherent or intrinsic dignity by the German term, “Menschenwürde.” In addition, he lists the dignity of merit, the dignity of moral stature and the dignity of identity. Dignity of merit refers to the dignity associated with rank or title, i.e., royalty, an elected official, a member of the clergy or a physician. The dignity of moral stature refers to the dignity attached to the character and conduct of one who is above reproach. Nordenfelt’s treatment of the dignity of identity is significant for patient care, inasmuch as it is concerned with the patient’s subjective sense of dignity.  

Especially useful to bioethics is Rentdorff’s description of seven functions of dignity. Rentdorff holds that dignity points to the special standing of humans in the universe, requires respect for the moral agency of individuals, rejects the notion that humans may be “commercialized” or assigned a monetary value, and expresses the idea that human beings are capable of shaping their own destinies. Dignity also functions to draw attention to a consideration of the effect of decisions or actions on self-esteem, restricts behavior that is uncivilized, and opposes treatment of others that is regarded as degrading. Also important to bioethics is an aspect of dignity which is perhaps implied in Rentdorff’s description of the seven functions, but not made explicit. Respect for the moral agency of individuals does not only mean respect for their right to make decisions, but also holding them responsible for their decisions and actions. Indifference to the content of decisions which have been made is not respect for dignity; holding persons accountable is.  

While the principle of dignity holds promise for the ethical analysis of upper extremity and facial VCA, it has received little sustained attention in the literature. Dignity is frequently referred to as being associated with bodily integrity, with the implication that it might be restored to recipients through successful VCA treatment. Concern about the psychological effects of disfigurement, disability and VCA reflect concern about subjective and social and relational (or attributed) dignity. Nordenfelt’s description of the dignity of identity specifically mentions
disfigurement and disability.\textsuperscript{389} Concern with dignity also appears in discussions of the necessary disfigurement of the donor, and efforts at cosmetic reconstruction of the donor after the retrieval of the grafts.\textsuperscript{390} Protection of the privacy and confidentiality of the donor, recipient and their families may also be seen as a means of respecting the dignity of those involved.\textsuperscript{391}

One major treatment of the theme of dignity in relation to facial VCA is found in a lengthy law review article by Rhonda Gay Hartman. Hartman argues that dignity should be the primary guide in determining whether and when facial VCA is appropriate.\textsuperscript{392} She discusses the dignity of donors,\textsuperscript{393} and concludes that reconstructive facial VCA can indeed promote patient dignity in some situations.\textsuperscript{394}

2.5.5.5 Vulnerability

The English word “vulnerability” is derived from the Latin vulnus, which means “wound”.\textsuperscript{395} Wounded persons are generally less capable than the unwounded of protecting themselves from additional harm. Some have linked vulnerability with autonomy, suggesting that “with reduced autonomy comes increased vulnerability”.\textsuperscript{396} This view has some merit, but is too narrow as a definition. While limited autonomy is one source of vulnerability, there are certainly other reasons why individuals or groups may not be in a position to protect themselves.

Vulnerability as an idea in modern bioethics goes back at least as far as the Nuremberg Code, where the call for consent should be understood to reflect concern about vulnerable persons as research subjects.\textsuperscript{397} Vulnerability entered the vocabulary of ethical codes with the \textit{Belmont Report}, and has since been included in major international statements on bioethics as the \textit{CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects}, the 2005 UNESCO

\textsuperscript{389}Nordenfelt, 76–77.
\textsuperscript{390}Lantieri, 252; Edwards and Mathes, 117; Coffman and Siemionow, 184.
\textsuperscript{391}Agich, 135.
\textsuperscript{392}Hartman, 80–91.
\textsuperscript{393}Hartman, 66–68.
\textsuperscript{394}Hartman, 77.
\textsuperscript{396}Hans Morten Haugen, “Inclusive and Relevant Language: The Use of the Concepts of Autonomy, Dignity and Vulnerability in Different Contexts,” \textit{Medicine, Health Care and Philosophy} 13 (2010): 203.

The Belmont Report is a product of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was established in the United States in 1974 with the passage of the National Research Act. The eleven members of the commission met for four days in February 1976 and produced a document that identified the ethical principles the commission felt should guide research with human subjects. The report attempts to set the boundaries between medical practice and medical research, delineate three basic principles (respect for person, beneficence and justice), and provide applications of the principles to research. It is under the heading of “Applications,” sub-section, “Selection of Subjects,” that vulnerability is mentioned. Specifically, concern is expressed over certain groups that might become targets for the recruitment of research subjects. Members of groups “such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized” are considered potentially “vulnerable subjects.”

Despite its origin in Belmont, the concept of vulnerability in bioethics has been more readily embraced internationally than it has in the United States. Beauchamp and Childress, the authors of the dominant American text in bioethics, begin to discuss vulnerability only in the sixth edition of their Principles of Biomedical Ethics. It is explored there in their chapter on “Moral Status,” where the authors address the issue of vulnerable populations over the course of a few pages. The term does not appear in the index or table of contents of Gert, Culver and Clouser’s Bioethics: A Systematic Approach or Veatch, Haddad and English’s Case Studies in Biomedical Ethics.

In contrast, the concept of vulnerability is quite extensively developed in two international bioethical resources. The CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects appeared in 2002. CIOMS, the Council for International Organizations of Medical Sciences, worked with the World Health Organization to develop this revision of earlier versions of international ethical guidelines for medical research. The CIOMS Guidelines address

399 Haugen, 208.
400 Beauchamp and Childress, 89–91. It seems likely that Beauchamp and Childress would consider the issues related to respect for vulnerability adequately addressed by their principles of respect for autonomy and justice.
vulnerability directly in Guideline 13, which states: “Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied”.

Just three years after the publication of the CIOMS Guidelines, UNESCO (United Nations Educational Scientific and Cultural Organization) published its *Universal Declaration on Bioethics and Human Rights*. Included therein is Article 8, which states:

> In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected.

The meaning of the article was set forth at length in the 2011 *The Principle of Respect for Human Vulnerability and Personal Integrity: Report of the International Bioethics Committee*. This latter document, in addition to providing a general introduction to the concept of vulnerability and an attempt to define the ‘determinants of ‘special vulnerability,’ offers a series of examples in place of a propositional definition.

In the 2008 update of the *Declaration of Helsinki*, vulnerability is addressed in articles 9 and 17. Approved at the 59th meeting of the World Medical Association, which took place in Seoul, Korea, the 2008 version is the sixth revision of the original statement created at the Helsinki meeting in 1964. Article 9 states: “Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.” In turn, Article 17 adds:

> Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

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404 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, 64.
408 2008 *Declaration of Helsinki*, 3.
In comparing the three international statements, it becomes clear that each uses substantially the same language to describe vulnerability and the obligations which respect for vulnerability entails.\textsuperscript{409}

As stated earlier, to be vulnerable is to be situated in such a way that one is, in one or more ways, unable to adequately defend against encroachments upon one’s person or interests. Given that the concern about vulnerability in bioethics was generated by historical occasions in which vulnerable persons were harmed, it is not surprising that vulnerability in bioethics carries a clear negative connotation. While acknowledging that vulnerability is universal, bioethics has focused its attention on groups and individuals who are especially vulnerable. Thus, vulnerability tends to be regarded in bioethics as an unfortunate and perhaps unjust condition, and the associated moral obligations tend to focus on either protecting the vulnerable or empowering them so they might be able to protect themselves.\textsuperscript{410} Special vulnerability, then, is seen to have certain “moral implications,” such as requiring extra justification for including vulnerable persons in research, offering special protections after vulnerable subjects are enrolled in research, and engaging vulnerable persons in research only when the research can be reasonably expected to benefit the subjects themselves or others similarly situated.\textsuperscript{411}

It is possible, however, to appreciate the continuity between ordinary and extraordinary vulnerability and to employ such an appreciation in the development of approaches to addressing conditions of special vulnerability. Such appreciation and approaches have been developed by Christian theologians, including William C. Placher,\textsuperscript{412} Ellen F. Davis\textsuperscript{413} and Kristine A. Culp,\textsuperscript{414} but may also be found in secular sources.\textsuperscript{415} These broader understandings of vulnerability will play a significant role in the construction of our concept of covenant consent later on.

\textsuperscript{409}Samia A. Hurst claims the European definitions tend to be much broader than those developed elsewhere, particularly in the United States. See Hurst, “Vulnerability in Research and Health Care; Describing the Elephant in the Room?” Bioethics 22, no. 4 (2008): 191–192.

\textsuperscript{410}See especially Articles 1–21 of The Principle of Respect for Human Vulnerability and Personal Integrity: Report of the International Bioethics Committee.


At this point, however, it is necessary to offer grounds for claiming that candidates for VCA may be regarded as being especially vulnerable. In the absence of clear, widely accepted criteria for what constitutes special vulnerability, the case must be made by assembling indicators from multiple sources. First, we will turn to the entry on vulnerability in the *Sage Handbook of Health Care Ethics*. Drawing upon the work of Kipnis, the authors offer a list of six categories of special vulnerability. From these six categories, at least two are potentially applicable to potential VCA candidates. These would include “medical vulnerability” and “social vulnerability”.

Medical vulnerability applies to candidates for VCA because it refers to persons who are so seriously ill or injured that they may be attracted to research protocols by unrealistic expectations. As Philip Nickel points out, “In general, research subjects tend to underestimate the level of risk or impact associated with participation in biomedical research,” while overestimating the likelihood of potential benefits. Subjects do so, Nickel claims, because of the effects of ‘‘motivated bias,’ i.e., errors based on a desire to believe something is true”. Given that those drawn to VCA tend to be those who have been unable to adapt to their disfigurement or disability, while others of equal or greater injury do adapt, the question is raised whether VCA inadvertently targets the most desperate among the disabled and disfigured who are also the most vulnerable.

Social vulnerability applies to candidates for VCA whose condition has led to social isolation. Facial defects often lead to such isolation. Upper extremity defects may also cause isolation, as a result of their effect on the individual’s self-image or because the functional consequences of the defect exclude the individual from certain activities. A sense of social isolation may also be created by the increased level of dependency that occurs as a result of a defect.

Loss of independence due to disability has been associated with a decrease in psychological well-being and subjective estimates of quality of life, a limitation of employment opportunities, and social stigma or marginalization. Persons with disabilities frequently “report giving up established ways of doing things, and

(Footnote 415 continued)


418 Rumsey, 22–23; Bradbury, 194.

419 Schenk, 411; Strong, 13; Rumsey, 22–23; Svenaeus, 144; 193–196; Bradbury, 193–196; Strandmark K., 142.

420 Examples would be the loss of the ability to continue one’s career, certain activities of daily living or familiar leisure activities.
forgoing numerous activities, plans and goals.” Various factors have been identified as playing a role in the subjective perception of dependence, including not only an individual’s pre-existing coping skills, but the “cultural norms and societal values” to which the individual has been exposed. When facial defects are of such a nature as to prevent normal eating or even normal breathing, and when upper extremity defects render persons unable (perhaps temporarily) to drive, feed themselves, etc., a state of dependency may be created which individuals may be so anxious to escape that they are willing to take greater than normal risks. Desperate individuals may also become prone to overestimating the potential benefits of proposed treatments.

The afore-mentioned Report of the International Bioethics Committee of UNESCO offers a number of examples of vulnerability in both straightforward healthcare and in research. Though none of these examples mentions VCA, they are by the authors’ own stated intention meant to be “neither exhaustive nor prescriptive,” but rather a means of “paving the way for a broader reflection…”

Among the examples that may be seen as reflecting the condition of potential candidates for VCA are the examples of “social vulnerability,” “premature applications of technology,” and “unexpected risks.” Social vulnerability in the report is substantially the same as social vulnerability described above. VCA could be regarded as a premature application of technology, given that the issues related to immunosuppression are not yet resolved sufficiently to justify exposing persons without a life-threatening condition to their toxic effects. VCA candidates could also be considered especially vulnerable because the “full risks of participation” are not known but are expected to be substantial, based on existing experience with SOT.

Both Diane Perpich and Rhonda Gay Hartman deal specifically with the implications of facial disfigurement for establishing a condition of special vulnerability. Perpich points out the obvious “link between the face and personal identity”

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422Eva Feder Kittay, “The Ethics of Care, Dependency and Disability,” Ratio Juris 24, no. 1 (2011): 55; Bradbury, 193; Svenaeus, 155; Rumsey, 22; Schenk, 411–412; Nickel, 256; Eileen Bradbury artfully remarks that patients who have received information about treatment burdens, risks and possible benefits “may have been listening through a filter of hope and distress.” Bradbury, 195.
which makes facial defects especially devastating and the promise of a transplant especially enticing.\textsuperscript{426} Perpich points out that functional limitations, such as the “inability to perform everyday actions such as eating or drinking, smiling or frowning” interfere with social interaction and deprive persons of vital social support.\textsuperscript{427} Thus, candidates for facial VCA are especially vulnerable, according to Perpich, and require a level of consideration, compassion and care beyond that otherwise expected in health care.\textsuperscript{428}

Rhonda Gay Hartman is more concerned with dignity than vulnerability, but the two are clearly related, as she acknowledges\textsuperscript{429} and the UNESCO IBC Report on Respect for Vulnerability and Personal Integrity asserts explicitly.\textsuperscript{430} Y. Michael Barilan sees vulnerability as “a derivative concept” grounded in “human dignity and human solidarity”.\textsuperscript{431} While granting that facial transplantation appears to offer “inestimable relief… for disfigured persons,”\textsuperscript{432} Hartman is cautious. She worries that “patient desperation and despair” will impede proper consent.\textsuperscript{433} Hartman also raises the issue of social vulnerability as a result of disfigurement, which may contribute to patient desperation.\textsuperscript{434} Social isolation, caused either by fear of rejection or the actual experience of it, can lead to feelings of hopelessness. She concludes that respect for human dignity and efforts to promote dignity are the best way to respond to the condition of vulnerability in the disfigured.\textsuperscript{435}

In light of the preceding discussion of categories and examples of special vulnerability, along with the review of the articles by Perpich and Hartman, it seems reasonable to conclude that candidates for facial and upper extremity VCA may be regarded as especially vulnerable. The consequence of regarding VCA candidates in this way is that they are therefore to be afforded special consideration, special protection and special support.\textsuperscript{436} That special consideration, special protection and special support may take several forms. In a later chapter, it will be argued that covenant consent is one possible form this special consideration, protection and support can take.

\textsuperscript{426}Perpich, 173–176.
\textsuperscript{427}Perpich, 176.
\textsuperscript{428}Perpich, 183–184.
\textsuperscript{429}Hartman, 59.
\textsuperscript{430}The Principle of Respect for Human Vulnerability and Personal Integrity: Report of the International Bioethics Committee.
\textsuperscript{431}Y. Michael Barilan, “Reflections on Human Vulnerability and the Rabbinic Perspective on Medical Ethics,” in Religious Perspectives on Human Vulnerability in Bioethics, 93.
\textsuperscript{432}Hartman, 64; 76.
\textsuperscript{433}Hartman, 72–74.
\textsuperscript{434}Hartman, 75.
\textsuperscript{435}Hartman, 90.
\textsuperscript{436}Strandmark K., 141–142; Perpich, 184; McLean, 106; Schenk, 413–414; Bradbury, 195–196; Hurst, 196–197; Rogers, Mackenzie, and Dodds, 24–26; Lange, Rogers and Dodds, 337.
2.6 Conclusion

This chapter has reviewed the historical background, origins and development of the practice of human vascularized composite allotransplantation of upper extremities and facial tissue. It has shown that technical skills and insights developed in the fields of solid organ transplantation, limb replantation and face replantation following partial or total avulsion have laid the groundwork for the development of upper extremity and facial VCA. The most significant among these technical skills and insights were the development of vascular and nerve anastomoses, microsurgical techniques, and a deeper understanding of the processes of immunological rejection. The development of VCA as a realistic clinical option had to wait, however, on the development of more effective and less toxic immunosuppressive agents and protocols.

As better immunosuppression was developed and implemented in SOT, VCA began to be seriously considered again. The potential for successful VCA was demonstrated first in an animal model. Eventually, the first human VCA were attempted. The first upper extremity transplant after the development of improved immunosuppression was attempted by Dubernard in 1998. Seven years later, Dubernard assisted Devauchelle in the first face transplant.

Since those pioneering efforts, many more surgeries of both types have been performed in several centers around the world. Despite generally good results thus far, a number of practical issues remain to be addressed in order to make the transition from small scale, experimental VCA to larger scale, routine clinical VCA. Among the issues are advances in tolerance induction, improvements in patient selection, the development of means to speed nerve regeneration and the establishment of best practices in rehabilitation and physiotherapy.

As facial and upper extremity VCA began on an experimental basis, it has been subject to close ethical scrutiny. The ethical issues raised by VCA are intertwined with some of the practical concerns, including especially the burden and risk to benefit ratio. The consideration of the burden and risk to benefit ratio must take into account the substantial negative side effects of immunosuppression, the potential for graft loss and what that might mean for recipients, the substantial duration and intensity of post-surgical physiotherapy, and psychological concerns. A general survey of the ethical debate thus far was presented, organized by ethical principles. These principles included respect for autonomy, beneficence, non-maleficence, justice, dignity and vulnerability.

The purpose of this chapter is to provide the first part of the foundation for an attempt to argue for the justification of a new form of consent, called covenant consent, for VCA procedures. The following two chapters will continue to build the

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foundation by exploring the history, development and current debate surrounding consent in bioethics and by examining the concept of covenant from its historical origins in the ancient near east through its development and applications in late twentieth and early twenty-first century bioethics. A thorough knowledge of all three subjects or areas is necessary before moving on to a description and justification of covenant consent for VCA.
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