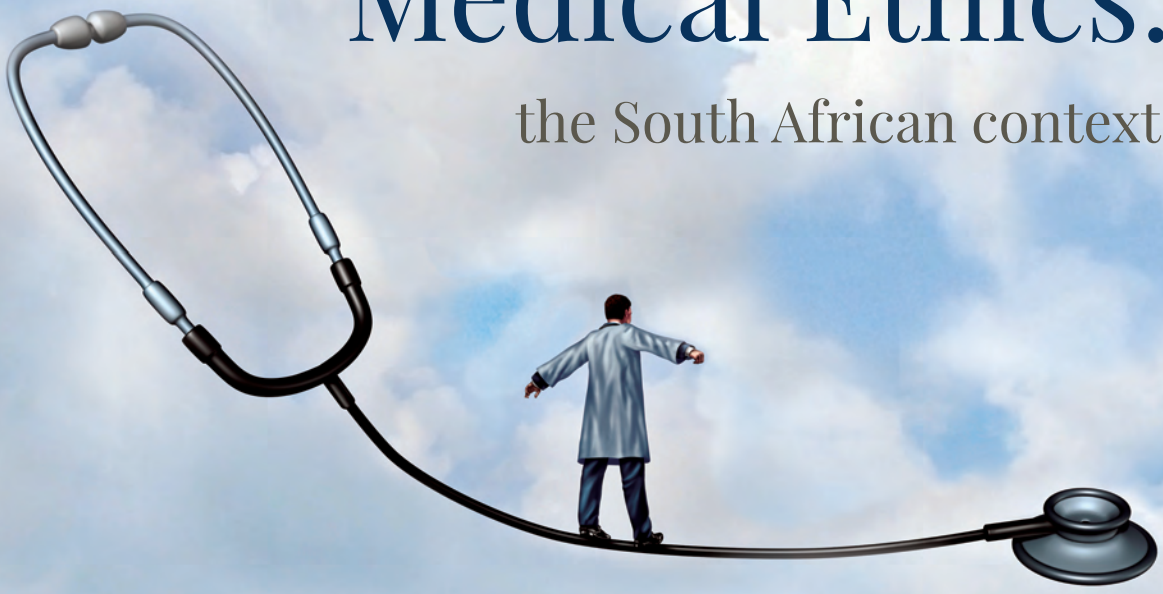
C. Jones, M. Kruger, J. van den Heever & A. van Niekerk (eds.). Challenges in Medical Ethics: the South African context. Stellenbosch: African Sun Media

Challenges in Medical Ethics:

the South African context



Editors:
Chris Jones, Mariana Kruger, Juri van den Heever & Anton van Niekerk

https://doi.org/10.52779/9781991201959/05

C. Jones, M. Kruger, J. van den Heever & A. van Niekerk (eds.). Challenges in Medical Ethics: the South African context. Stellenbosch: African Sun Media

5

Ethics of Transplantation

Willie Koen

Keywords: artificial mechanical circulation; cadaver organ transplantation; Hippocratic oath; ethical challenges; lifesaving and non-lifesaving organ transplantation; living donor organ transplantation; stem cell transplantation; transplant waiting list; Xeno transplantation

5.1 INTRODUCTION AND GENERAL CONCEPTS IN TRANSPLANTATION

The first recorded attempt of human organ transplantation in 1934 opened a new chapter in the field of ethics. Transplantation is regarded as a medical procedure where the aim is, primarily, to improve the quality of human life and, secondarily, to improve the long-term outcome of the patient. The donor organ can be harvested either from a brain-dead human, also referred to as cadaver donor organs, or from a live human such as a family member, referred to as living related donor organs. In the case of cadaver organs, the donor organs can be harvested from a brain-dead, beating-heart donor or a non-beating-heart donor. Where a donor organ is harvested from a living donor, the donor can be either related or unrelated to the recipient.

Organs for transplantation can further be divided into solid organs such as heart, lungs, kidney, and liver, or non-solid organs such as bone marrow, corneas, or bone.

Lifesaving organ transplants include heart, lung, or liver transplants where a patient will not only have an improved quality of life but will also have the additional benefit of increased life expectancy. In non-lifesaving organ transplant ation such as limb, face, uterus, and penis transplants, the patient can only expect an improvement in quality of life.

https://doi.org/10.52779/9781991201959/05

The main obstacle of successful human transplantation is donor organ rejection by the recipient. This is a phenomenon where the immune system of the recipient identifies the donor tissue as foreign and launches an immune response in an effort to remove this foreign tissue from the body. This is a similar response that the body will have to unwanted bacteria, viruses, or foreign bodies. This response eventually leads to the cessation of function of the transplanted organ. To counter this immune response, all transplantations require some form of suppression of the immune system. This is done by immunosuppressing medication, also referred to as anti-rejection medication. In the early days of transplantation, the main immunosuppressing medication was cortisone and the outcomes in, for instance, heart transplants, resulted in a one-year survival of hardly 30%. In 1984, a novel medication belonging to the group of calcineurin-inhibitors, namely cyclosporine, was discovered. This anti-rejection agent revolutionised the outcomes of organ transplantation and one-year survival rates of more than 90% have been seen since. Unfortunately, all anti-rejection medication has side effects, either due to direct toxicity or indirectly due to the long-term suppression of the immune system. This direct toxicity of these agents has a damaging effect on other organs, especially the kidneys. In contrast, the indirect complications of anti-rejection medication involve the suppression of the immune system, which prevents the immune system from functioning at its full capacity and leads to the inability to fight bacteria and viruses which eventually leads to infection. Furthermore, an important function of the immune system is to identify abnormal cells in the body such as rapid duplicating cells, more commonly referred to as cancer cells. As a result, anti-rejection medication can indirectly lead to cancer in the transplanted patient. For instance, in cardiac transplantation, malignancy and infections are the cause of 40% of the mortality by ten years after the transplant.

Therefore, finding a balance between under- and over-suppression of the immune system is a critical challenge in the management of the transplanted patient. As a result, these facts lead to a key question in transplantation: do the risks of the transplant with its subsequent complications, especially due to the immuno-suppressing agents, outweigh the risk of not performing the transplant?

5.2 CADAVER ORGAN TRANSPLANTATION

Before organs from a cadaver can be harvested from a deceased person, either in the case of a beating-heart or non-beating-heart situation, the necessary consent should be obtained from the donor (Groth, 1972). As the donor has ceased to exist as a person, the last wish of the donor should be considered. This wish of the donor could have been recorded at some stage in a legal document such as a

https://doi.org/10.52779/9781991201959/05

will and, if not, the next of kin can give consent to proceed with the organ donation process (Siminoff, Agyemang & Traino, 2013).

Due to factors such as the stability of the donor, the timeframe to harvest these organs is limited to hours. Therefore, waiting until the legal will of the patient is read and executed is not a practical option. For this reason, family consent is the norm in most transplanting countries, including South Africa. This is referred to as the "opt-in" system. Alternatively, with the "opt-out" system that is utilised in certain countries such as Spain, all citizens are regarded as organ donors unless there is an objection from the donor, for instance by a legal will of the donor. As many potential donors are lost due to failure to obtain consent, either due to difficulty in locating the family or due to a bereaved and traumatised family that cannot make a decision in this critical instance, the "opt-out" system leads to a higher donor organ yield. However, in countries such as South Africa, where there is a population with diversity in religion, cultures, and traditional beliefs, the "opt-out" system can, arguably, not be implemented, as it cannot be assumed that the general bias of the population is towards organ donation (Editorial, 2017).

In beating-heart organ donors, the donor is still in full physiological function but is brain dead. Brain death can be defined as irreversible brain damage with the loss of all brain stem activity and therefore voluntary or involuntary functions (Sarbey, 2016). This means that the patient is unable to breathe spontaneously (apnoea). For this reason, the donor is connected to a ventilator to maintain respiratory function, which is to supply oxygen to the blood. In the absence of oxygen in the circulation, also referred to as ischaemia, all organs will stop functioning over a period of minutes. For organs to be used in transplantation, these organs should be fully functional and undamaged, especially from ischaemia. In the case of non-beating-heart donors, the heart has already stopped, and organs are then harvested (Ridley et al., 2005). This situation occurs when the patient was unstable and cardiac function could not be maintained. This period where the heart has stopped has to be short as the absence of blood circulation will lead to organ ischaemia.

As the heart has the highest oxygen extraction rate of all organs in the donor, ischaemia will set in first in the heart and damage to the heart muscle starts seconds after the heart has stopped. Adding the time of the explanation procedure to this, which takes around an hour, the heart will sustain significant ischaemic damage. To overcome this delay, the patient can be connected to an extra-corporeal oxygenation mechanical circulation to minimise organ ischaemia.

Nevertheless, in cardiac transplantation, a non-beating-heart donor is a sub-optimal option and the outcomes of the transplant will be significantly compromised.

https://doi.org/10.52779/9781991201959/05

In contrast, in renal transplantation, the kidney can tolerate a short period of ischaemia better, although it is arguably still not an ideal situation. However, due to the shortage of organ donors, non-beating-heart donor organs are considered in many renal transplant centres around the world in special cases as an attempt to increase the donor organ pool. The dilemma faced by the renal transplant team is to weigh the risk of a non-beating-heart kidney against not performing the procedure at all. This is a debatable situation as the renal patient can still be maintained on a renal dialysis machine which serves as an artificial kidney and can maintain the patient. However, this dilemma can then be further complicated as there are only limited dialysis slots available due to the limited number of dialysis machines. It can therefore be argued that a patient who receives a kidney transplant will at least make a dialysis slot available for another patient in end-stage renal failure. Another consideration in non-beating-heart donation questions the absence of mechanical circulation oxygenation. In this situation, the absence of supporting the circulation of the non-beating-heart patient results in the ethics of the situation being challenged, because it is argued that the patient can still be neurologically not brain dead as brain dead testing requires a repeat evaluation 12 hours after the initial testing to confirm brain death (Mohamed, Verheijde & McGregor, 2007).

TABLE 5.1 Modified Maastricht classification of non-beating-heart donors (Kootstra et al., 1995)

Category I	Dead on arrival
Category II	Unsuccessful resuscitation
Category III	Awaiting cardiac arrest
Category IV	Cardiac arrest in a brainstem-dead donor
Category V	Unexpected cardiac arrest in a critically ill patient

5.3 LIVING DONOR ORGAN TRANSPLANTATION

In living donor organ transplantation, the organs are harvested from a live donor as opposed to cadaver organs as described earlier. For instance, as a patient has two kidneys and can function normally with one kidney, the other kidney can therefore be donated. However, in heart, liver, and lung transplantation, living donors cannot be used for obvious reasons. Nevertheless, part of an organ such as a lobe of the lung or liver can be donated (Broelsch, Testa, Alexandrou & Malagó, 2002).

As this is not the full organ, this portion or lobe will usually not be sufficient for an adult recipient and can be used, for instance, in a child or a very small adult.

https://doi.org/10.52779/9781991201959/05

The ethical dilemma lies in the relationship between the live donor and the recipient. In the case where there is a direct family relation or genetic relation, the motive for the donation of the organ by the donor can be assumed as benevolent. However, in the case where there is no family relation, benevolence cannot be assumed (De Groot, Van Hoek & Hoedemaekers, 2015).

This opens the discussion for donation of organs for compensation. Opponents of organs for compensation will argue that it can lead to exploitation of the poor and those in desperate need of money. Furthermore, organ trafficking is a reality where the donor is exploited to the advantage of the trafficker and the recipient. Even the donation of organs between wife and husband can later lead to a contentious situation after, for example, a divorce. However, proponents of organs for compensation will argue that it is not uncommon for employees to sacrifice their health for compensation, for example mine workers who are exposed to dust inhalation and subsequent pulmonary disease (Dalal, 2015).

5.4 ALLOCATION OF CADAVER ORGANS IN TRANSPLANTATION

When a potential donor is identified in a health facility, the donor organ procurement team is contacted. In South Africa, there is a network of organ donor coordinators in the five major cities of the country. The donor coordinator then liaises with the referring facility and gets the status of the donor. This includes the cause of brain death, confirmation that the necessary brain death testing has been carried out, as well as the donor's clinical status, weight, and blood group.

The coordinator usually obtains informed consent from the family. Once it has been confirmed that the patient fulfils the criteria to be a donor, the coordinator contacts the relevant organ transplant programmes. Each organ transplant fraternity has their own allocation system in South Africa. In the United States and Europe, there is a central organ registry that allocates organs. This means that the donor coordinator refers the donor organs to the central organ registry and on acceptance will allocate the organs to a recipient according to a protocol. The demographics, size of the country, and population distributions vary in different parts of the world and therefore different protocols are used. The type of organ referred is also allocated according to the protocol for that specific organ.

In South Africa, the vast differences and limited transplant programmes make the use of a single centralised organ allocation initiative unpractical. Each discipline, namely the cardiac, lung, and renal programmes, has their own collaborative allocation protocol which has been decided by each discipline. For instance, if a donor becomes available in a city, the heart will first be offered to the centre

https://doi.org/10.52779/9781991201959/05

that procured the organ. The transplant surgeon can accept the heart unless there is an urgent priority listing at another centre. The priority listing is shared by all cardiac programmes and is updated weekly. Should the transplant surgeon not be able to use the heart for reasons such as a blood group mismatch or size mismatch, the organ will then be referred to the next programme in that city. Should this programme also not be able to use the organ, the organ will be referred to a programme in another province. As explanted organs have a limited safe timeframe before it has to be implanted, it makes sense that organs must be referred to local centres first. However, in the situation where there is a recipient on the urgent priority waiting list, the risk of the longer distance harvest will be considered and weighed against the urgency of the patient. Therefore, in organ allocation, the key consideration of risk of transplantation versus not doing the transplant comes to the fore again. This can lead to the dilemma of comparing the status of two urgently listed patients from different centres. In such a case, the surgeons of the respective programmes will contact each other and discuss the urgency of their listed patients to come to a mutual decision.

5.5 TRANSPLANT WAITING LIST

Age cut-off policies have been an ethical issue for decades in the transplant community. The argument is that in contrast to younger patients, older patients might have more risk factors for a transplant, have already enjoyed years of living, and are usually no longer the breadwinners. Furthermore, due to the shortage of donor organs, the bias is towards younger patients. For these reasons, the age cut-off for heart transplant recipients in North America and Europe is 60 years. However, in South Africa, due to the relatively smaller transplant programmes, a situation often arises that a donor heart cannot be used for various reasons among all the programmes. In this instance, the donor organ is sadly wasted. Also, as South Africa is the only country on the continent doing heart transplants, such a donor heart cannot be shipped to a neighbouring transplant country as is the case in Europe. To send the donor heart to, for instance, Europe is also not an option as the time frame of the donor heart outside the body is limited to four hours. For this reason, the age cut-off for heart recipients in South Africa is 65 years with the understanding by the recipient that younger patients could be considered first.

When a patient is confirmed to be a suitable recipient candidate, the next step is to add the patient to a waiting list. An important consideration is to establish the urgency of the need for the transplant and therefore a timing for the procedure can be envisaged. This is usually a 'wait-and-see' approach as patients can either

https://doi.org/10.52779/9781991201959/05

deteriorate more rapidly than expected or even improve due to optimisation of the medication. For this reason, the patient on the waiting list must be assessed frequently to establish the clinical progression of the condition. In cardiac transplantation, this is a challenge as the progression of the underlying heart failure is temperamental.

With regard to considering when to put a patient on the waiting list, the fact that it can take up to one year for a suitable donor heart to become available must be considered. Centres often have an 'active' waiting list and a 'cold' list. Patients on the active waiting list are regarded to have a high mortality of 80% over the next year unless a transplant is performed. Should the joint view be that a patient has a stable condition with poor heart function but is still coping and should not have very high mortality in the next 12 months, then the patient will be placed on the cold list. When a donor heart becomes available, only patients on the active waiting list will be considered. However, should a patient's condition on the cold list deteriorate, then the patient can be moved onto the active waiting list.

To allocate a donor heart to a patient on the active waiting list requires some consideration. The blood group is the first consideration as this should be compatible. This is referred to as ABO-compatibility and represents the different classes of blood groups. The patients on the list that match the blood group will be considered. This sub-group will then be further assessed by using weight and size. It is important to use a donor heart of similar size to optimise the outcome. This will therefore eliminate more patients in the sub-group. From here, the remaining candidates will be considered according to the criticality of their conditions. The more critical patients will be considered. Should the patients be of the same clinical status, other factors such as the period on the waiting list, age, and social status of the patient and distance of harvesting will be considered. Therefore, contrary to common understanding, the patient who has been on the waiting list the longest is not necessarily the next candidate to receive the next donor heart. Unfortunately, this prioritisation of recipients can open an opportunity for manipulation and foul play (Connolly, 2013).

5.6 ARTIFICIAL MECHANICAL CIRCULATION

The search for a mechanical solution for end-stage cardiac failure started before the era of heart transplantation. However, since the first heart transplant, the majority of research continued in transplantation rather than finding a mechanical solution. Nevertheless, the rapid advances in technology have led to major progress in mechanical cardiac support. This research was also encouraged by the

https://doi.org/10.52779/9781991201959/05

realisation that donor organ supply will always be a limiting factor and waiting periods for donor organs are a major disadvantage. This vision of having mechanical devices readily available on demand, as well as a gradual improvement in clinical outcomes, has developed to a point where mechanical heart implantation has the same two-year outcome as a human heart transplant.

The additional advantage of the mechanical device is that it can stabilise the recipient in desperate need of a heart and that the recipient can now safely wait for a donor heart. These devices are implanted into the heart but is still connected to an external battery-control system. This external hardware is a limitation to the patient as it needs daily charging. But, because these devices are made from biological inert material, rejection, which is encountered in organ transplantation, is not an obstacle and no anti-rejection medication is needed. These devices can support patients over several years and outcomes of over 10 years are often seen. Currently, the main indication for a mechanical heart device is a patient who is on the heart transplant waiting list and deteriorating, with the availability of an urgent donor heart not envisaged. Other indications would be other reasons for not qualifying for an organ transplant such as age cut-off or antibodies.

Once the patient has received a mechanical device, the patient can remain on the transplant waiting list. The dilemma then becomes whether the patient should have a lower priority for transplantation as the patient is now in a better clinical situation, or whether the priority should remain the same. As discussed earlier, the primary consideration to allocate a donor heart to the sickest patient can result in the patient who is now more stable on the mechanical device to face a much longer time waiting for a donor heart.

Arguably, a donor transplant is still the gold standard and mechanical devices do have complications of their own. Therefore, waiting to the point where complications set in as a result of the mechanical device can lead to the same initial dilemma of needing an urgent organ. It is therefore paramount that the patient on the mechanical device is frequently monitored to ascertain at which point the patient should be put back onto the active heart transplant waiting list, thereby having the same priority as other waiting recipients.

Another dilemma is that a mechanical heart could have been inserted into a patient where the patient was still within the age cut-off point. Should the patient have this device in for several years, it could take the patient over the cut-off age for transplantation, therefore the patient might not qualify according to the accepted age definition for a heart transplant. In these cases, the clinical status of the patient should be assessed, and should the patient still be eligible for

https://doi.org/10.52779/9781991201959/05

an organ transplant, except for the age limit, most programmes will accept the patient onto the active waiting list regardless of age.

Another aspect of these devices is that a device can be implanted as a "bridge-to-transplant", meaning that it is a temporary strategy with transplantation as the end goal. The concept "destination therapy" refers to the strategy where a device is implanted but a later transplant is not planned.

A further dilemma is the cost of these devices. These devices are expensive, similar to that of a luxury motor vehicle. Being readily available and not governed like organ transplantation by the shortage of donor organs, many of these devices can be potentially implanted and can be a massive burden on a national health budget. For this reason, many countries, such as the United Kingdom, do not allow funding for mechanical devices as destination therapy unless it is privately funded. In such cases, it can be argued that destination therapy is only available to the wealthier society.

5.7 STEM CELL TRANSPLANTATION

The successful treatment of using human stem cells (hSC) is well recognised. Especially in bone marrow conditions and cancer treatment like leukaemia, this has proven a successful treatment modality (Chu et al., 2020). As stem cells have the potential to differentiate into other cell lines such as neural tissue, myocardial cells, or blood cells, the potential to use stem cell therapy in conditions such as heart failure, Parkinson's disease, and diabetes has been researched (Hwang, Varghese & Elisseeff, 2008).

Stem cells can be obtained from the person itself who requires the treatment and is referred to as autologous adult stem cell transplantation. In the case where stem cells are used from a different person, this is referred to as allogenic stem cell transplantation. Adult stem cells and stem cells from umbilical cord blood are multipotent cells, meaning they have the potential to differentiate, with the necessary manipulation, into other stem cell lines such as neural tissue or myocardial tissue. The practical principle of this treatment modality is to inject these cells into damaged areas such as the heart and allow the stem cells to differentiate into myocardial tissue and thereby repair the damaged areas (Gratwohl, Pasquini & Aljurf, 2015).

This strategy is still in an experimental stage and gives hope that eventually damaged organs can be repaired rather than transplanting the entire organ. However, there are also concerns with such treatment, for instance the risk that the stem cells might not differentiate into the desired tissue or can even lead to

https://doi.org/10.52779/9781991201959/05

excessive differentiation which can lead to tumours (Kanagasundram & Amini, 2018). However, obtaining these adult cells is a relatively easier process than other forms of obtaining stem cells.

Stem cells can also be obtained from embryos, referred to as human embryo stem cell transplantation (hESC). However, this strategy is fraught with ethical issues. In contrast to adult stem cells, these cells have a better potential to differentiate into the desired tissue line. With hESC, the stem cells are obtained from the early stage of an embryo. After the fertilisation of the oocyte, the cells duplicate to form an early embryo also known at this stage as a blastocyst which usually contains five to six cells. It is from this stage onwards that the main lines of human tissue develop. This process can be done as an in vitro process in a laboratory (Vazin & Freed, 2010). Nevertheless, it still requires a human oocyte which has to be donated by the female human. It is at this point where the ethical dilemmas in hESC transplantation come to the fore.

The first argument is that an embryo is an early human being and therefore human life is sacrificed. The debate continues – at which stage does an embryo become a person? This debate has been going on for decades as there is strong public support that once an oocyte is fertilised, human life has begun. This view has been challenged by the fact that these cells often do not continue to grow, can form into multiple cells (in the case of twins), and cannot be defined as a person at that early point. The debate goes on (Assen, Jongsma, Isasi, Tryfonidou & Bredenoord, 2021).

The irony in many of these debates is the fact that it overlooks the situation where a large percentage of females in the world are using oral contraceptives for birth control. These contraceptives have different mechanisms of action, whereby one such action prevents the fertilised oocyte from attaching to the inside of the uterus (endometrium) and therefore preventing a pregnancy. The human oocyte is therefore also sacrificed (Rivera, Yacobson & Grimes, 1999). Therefore, the view of "sacrifice life to save life" is still a contentious debate in the world of hESC research.

A further ethical problem involves informed consent for the donation of tissue for stem cell research. As there is a wide difference in opinion of members of the public on stem cell research, it cannot be assumed that all members of the public agree on all the modes of stem cell research. For instance, a person might agree on research for cancer treatment but might not necessarily agree on aspects such as financial gain from this research. These aspects should be included in the informed consent given by the donor (Caulfield, Ogbogu & Isasi, 2007). A further dilemma is confidentiality in stem cell donation. Donors

https://doi.org/10.52779/9781991201959/05

have the right to confidentiality of personal information which could be used in later discrimination towards donors by anti-stem cell activists (Snyder & Loring, 2006).

Another strategy in stem cell research is the reprogramming of the oocyte (egg cell) by transplanting the genetic DNA from the nucleus of a donor cell into the recipient oocyte. As a result, an embryo with a different genetic code can develop. This process is referred to as somatic cell nuclear transfer (SCNT). This has been successful and had wide media coverage when Dolly the sheep was cloned in 1996 (Campbell, McWhir, Richie & Wilmut, 1996). In 2013, the first human embryonic stem cells derived by somatic cell nuclear transfer were described (Tachibana et al., 2013). This reprogrammed oocyte can then be transferred back into a surrogate and allowed to develop to maturity. An application of this strategy could be used to produce animals such as pigs with a gene code of which organs can be used to be transplanted into humans.

It is evident that there are many ethical dilemmas to be considered in SCNT. One such dilemma could be to ask to what extent can the oocyte be reprogrammed and what would be the purpose of the end creature that is developed. This could for instance lead to the development of an embryo and subsequently a mature animal with two sets of DNA also known as a chimera. This process of chimerism is well established and already in clinical use in human stem cell treatment in bone marrow transplantation. This is a process where the diseased bone marrow of a patient is replaced by donor bone marrow to produce blood cells. After the transplant, the patient with their DNA will have circulating blood cells with a different DNA (Bader, Niethammer & Willasch, 2005). The ethical dilemma comes when the chimerism is between two different species and the possibility to create a 'half man, half beast'. This is referred to as interspecies chimerism. Although the motive behind this form of chimerism is intended for medical treatment, such as producing organs or body parts for humans to be grown from animals, the fear of abuse of this science cannot be overlooked.

5.8 XENO TRANSPLANTATION

Cross-species organ transplantation is referred to as Xeno transplantation. The idea of using animal organs to improve the lives of humans has already been described in 1667 when French physician, Jean-Baptiste Denis, transfused 12 ounces of blood from a lamb into a feverish young man (*Encyclopaedia Britannica*, n.d.). In the 1960s, Keith Reemtsma implanted 13 human patients with chimpanzee kidneys (Reentsma et al., 1964). During the same period, James

https://doi.org/10.52779/9781991201959/05

Hardy implanted the first chimpanzee heart into a human. The organ failed after a few hours (Hardy et al., 1964).

In 1977, Christiaan Barnard implanted two animal hearts into two patients. The first was a baboon heart which failed some hours after the implant and the second was a chimpanzee heart which was implanted as a heterotopic transplant. The patient died after four days as the patient's own heart did not recover (Barnard, Wolpowitz & Losman, 1977; Brink & Hassoulas, 2009).

The reason why xenografts fail and have not yet become a recognised source for human transplantation is that the animal organ excites a strong immune response in the human against this foreign tissue and leads to acute rejection. The current anti-rejection strategies and medication used in human-to-human transplantation are not effective to ensure a viable transplanted xenograft.

In 2022, the first pig-to-human heart transplant using a heart from a genetically modified pig was performed. At the time of writing, the patient was still doing well after the surgery (Reardon, 2022).

As the main limitation in the field of transplantation is the shortage of donor organs, this latest breakthrough in Xeno transplantation has given this field new hope as a future option in organ supply. However, this latest strategy to use genetically modified animal organs will have to prove itself against existing modalities such as human organ transplant and readily available mechanical heart options. The current outcome of a human/mechanical heart has a one-year survival of more than 90% and a two-year survival of 85%. The question is whether genetically modified animal organs will ensure similar results. It would be ethically difficult to implant a patient if these other two methods are available in the absence of long-term results of xenografts. Until it has proved itself, genetically modified xenografts can only be used when the other two options are not available or contra-indicated.

As far as animal rights and ethics in the use of animals as organ donors are concerned, the two main groups of animals considered for Xeno transplantation are the non-human primates such as chimpanzees, gorillas and baboons and large non-primates such as pigs. In the first group, the concern is that these animals have a closeness to humans and more developed feelings. They breed slowly and err on the brink of extinction and are not sacrificed for human consumption but rather conserved. In the latter group, these animals are too distant to evoke the same feelings and can breed rapidly. Currently, pigs are the most consumed large animal in the world. It can be expected that fewer ethical dilemmas will arise in using the latter group as a source of donor organs. As the field of Xeno

https://doi.org/10.52779/9781991201959/05

transplantation was to date purely a field of research, recent breakthroughs will elicit the need for interfraternal discussions and the publication of guidelines to address these challenges.

5.9 NON-LIFESAVING ORGAN TRANSPLANTATION

When organs are transplanted to improve the quality of life rather than saving the life of the patient, it is generally referred to as non-lifesaving transplantation. This form of transplantation includes limb, face, penis, and uterus transplantation. As mentioned earlier in this chapter, all forms of transplants are subjected to the process of immunorejection and will require anti-rejection medication to ensure a viable implant. However, these drugs come with their own complications such as renal toxicity, hepatic toxicity, and neuro toxicity. It also has secondary complications due to the suppressed immune response and predisposes the patient to infections and malignancies. The primary consideration in all forms of transplants holds here too, namely: the risk of the procedure vs the benefit.

5.9.1 Penile transplantation

The first penis transplant was reported in 2006 but the procedure was reversed only fourteen days after the transplant (Hu et al., 2006). In 2015, Andre van der Merwe performed the world's first successful penis transplant in Tygerberg Hospital, Cape Town, South Africa. The patient had a speedy recovery and could have sexual intercourse after three months. No major complications were reported in the first 24 months other than reversible anti-rejection agent induced renal impairment (Van der Merwe et al., 2017).

As the indication for penile transplantation is not necessarily lifesaving, many debates have followed since the first procedure. The risks of a long-protracted operation which can include septicaemia and even death have been raised in addition to the side effects of anti-rejection medication which include renal failure, sepsis, and malignancies. However, the protagonists point out that the absence of a penis not only increases the risk of urinary tract infections but may also have psychological impacts on a person. This could lead to lifelong psychological trauma and even suicide. In certain cultures, such as traditional Chinese thinking, the penis is seen as the 'life-spring' essential to carrying on the ancestral line. The following guiding principles have been suggested by Zhang, Zhai and Hu (2010):

1. Penile transplantation should be performed only in patients with severe damage to the penis.

https://doi.org/10.52779/9781991201959/05

2. Penile transplantation should be done in appropriate institutions under the protocols approved by institutional review boards.
3. Institutions should have surgical and transplantation expertise, and transplantation teams should include multidisciplinary experts such as plastic surgeons, immunology/transplant specialists, infectious disease and oncology specialists, medicolegal experts, physical therapists, pharmacology specialists, patient advocates, and media relations representatives.
4. Appropriate selection criteria should be established, and the risk/benefit ratio must be considered for each individual patient.
5. Patients and their families should be presented with special informed consent documents explaining the risks, benefits, alternatives, and innovative nature of the procedure.
6. Candidates for penile transplantation should undergo a thorough psychiatric and psychological evaluation, including evaluation of their psychosocial support system.
7. Patients with known psychological and psychiatric diagnoses, poor coping skills, poor support systems, or a history of noncompliance are poor candidates for penile transplantation.
8. Due to the novelty of the procedure, proceeding in incremental steps and gathering more evidence from research done in the field are necessary to ensure its appropriate application.
9. Peer review of the penile transplantation procedure is mandatory to ensure compliance with medical standards of care and objective assessments of the outcomes.
10. The ethics of performing a new procedure with unknown outcomes must be carefully assessed and weighed against potential benefits to the selected group of patients with severe penile damage following the evaluation of such candidates for penile transplantation by medical ethics specialists.

Therefore, the ethical consideration in penile transplantation will be again the basic question: is the benefit worth the risk? From the considerations mentioned above, it is clear that the importance of a penis can be viewed by the individual differently. This difference in views will depend on the age of the patient, culture, and also the joint view of not only the patient but also the partner. It will be important to view each case individually rather than having a dogmatic approach. A multidisciplinary panel approach is key in the consideration of this treatment.

https://doi.org/10.52779/9781991201959/05

5.9.2 Facial transplantation

In 2005, the first partial face transplant was reported in France on a 39-year-old woman whose face was mauled by a dog. Her nose, lips and chin were transplanted from a cadaver donor, and she required anti-rejection medication (Rifkin et al., 2018). Her face was reported to have been rejected ten years later. She died a year later from cancer which was reported as a complication from anti-rejection therapy (Jouan, 2016). Since this initial ground-breaking procedure, many more facial transplants which also included full-facial transplants were performed. The ethical dilemma in this case boils down to the question if the face transplant was worth the nine years of survival just to die at the age of 49. This was nine years of intense immune therapy, a high-cost burden with a relative improvement in facial appearance. During this period, she could not bear children as it is contra-indicated in patients on anti-rejection therapy, required to frequently attend the transplant clinic which entails numerous blood tests and investigations. One can also ask if other options such as reconstructive surgery was not an alternative?

Nevertheless, a patient still possesses autonomy in decision-making but with the proviso that the patient was fully informed of the outcomes before giving consent to such therapy. Also, how much weight can be placed on a patient's ability to make decisions in a traumatised psychological state and the role of the health care worker with the professional foreknowledge which can assist her decision at the time.

5.9.3 Uterus transplantation

Another form of non-lifesaving transplantation is the transplantation of a uterus for the purpose to bear a child. The main indications include an absent uterus, or malformed or diseased uteri. The first successful transplant of a uterus to bear a healthy child was reported in 2014 (Akouri, Maalouf & Abboud, 2020).

In 2021, it was reported that since the first successful implant, 45 uterus transplants have been performed worldwide with nine live births (Jones, Saso & Bracewell-Milnes, 2019). Other options for acquiring motherhood include surrogacy and adoption. Ethical questions that have been raised include, for instance in the UK, the number of children put up for adoption is increasing in contrast to the decreasing number of adoptions (Department for Education England, 2019). Surrogacy is well established, and thousands of children have been brought into life with this strategy (Perkins, Boulet, Jamieson & Kissin, 2016). Uterus transplantation can also be extended to transgender individuals or even men which will allow them to bear children. In the case of uterus transplantation into

https://doi.org/10.52779/9781991201959/05

men or transgender women, new concepts of being a 'mother' or 'father' will need to be defined (O'Donovan, Williams & Wilkinson, 2019).

As the uterus transplant is a temporary undertaking, anti-rejection agents with known long-term complications such as renal failure and malignancies become less contentious as the anti-rejection medication is a temporary requirement.

5.10 CONCLUSION

The field of transplantation is fraught with ethical challenges. However, these challenges can be addressed and overcome by using the fundamental question of "risk versus benefit". Furthermore, the first part of the Hippocratic oath of the medical profession still forms the basis of any medical intervention namely, "do no harm". Doctors are brought up to always consider the four main principles of medical ethics: *respect for autonomy*, *beneficence*, *non-maleficence*, and *justice*.

https://doi.org/10.52779/9781991201959/05

Bibliography

Akouri, R., Maalouf, G. & Abboud, J. 2020. First live birth after uterus transplantation in the Middle East. *Middle East Fertility Society Journal*, 25:a30. https://doi.org/10.1186/s43043-020-00041-4

Assen, L.S., Jongsma, K.R., Isasi, R., Tryfonidou, M.A. & Bredenoord, A.L. 2021. Recognizing the ethical implications of stem cell research: a call for broadening the scope. *Stem Cell Reports*, 16(7): 1656-1661. https://doi.org/10.1016/j.stemcr.2021.05.021

Bader, P., Niethammer, D. & Willasch, A. 2005. How and when should we monitor chimerism after allogeneic stem cell transplantation? *Bone Marrow Transplant*, 35:107-119. https://doi.org/10.1038/sj.bmt.1704715

Barnard, C.N., Wolpowitz, A. & Losman, J.G. 1977. Heterotopic cardiac transplantation with a xenograft for assistance of the left heart in cardiogenic shock after cardiopulmonary bypass. *South African Medical Journal*, 52:1035-1039.

Brink, J.G. & Hassoulas, J. 2009. The first human heart transplant and further advances in cardiac transplantation at Groote Schuur Hospital and the University of Cape Town – with reference to: the operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. *Cardiovascular Journal of Africa*, 20(1):31-35.

Broelsch, C.E., Testa, G., Alexandrou, A. & Malagó, M. 2002. Living related liver transplantation: medical and social aspects of a controversial therapy. *Gut*, 50(2):143-145. https://doi.org/10.1136/gut.50.2.143

Campbell, K.H.S., McWhir, J., Richie, W.A. & Wilmut, I. 1996. Sheep cloned by nuclear transfer from a cultured cell line. *Nature*, 380:64-66. https://doi.org/10.1038/380064a0

Caulfield, T., Ogbogu, U. & Isasi, R.M. 2007. Informed consent in embryonic stem cell research: are we following basic principles? *Canadian Medical Association Journal*, 176(12):1722-1725. https://doi.org/10.1503/cmaj.061675

Chu, D.T., Nguyen, T.T., Tien, N., Tran, D.K., Jeong, J.H., Anh, P.G., Thanh, V.V., Truong, D.T. & Dinh, T.C. 2020. Recent progress of stem cell therapy in cancer treatment: molecular mechanisms and potential applications. *Cells*, 9(3):563. https://doi.org/10.3390/cells9030563

Connolly, K. 2013. Mass donor organ fraud shakes Germany. *The Guardian*. [Online]. 9 January.

Dalal, A.R. 2015. Philosophy of organ donation: review of ethical facets. *World Journal of Transplantation*, (2):44-51. https://doi.org/10.5500/wjt.v5.i2.44

De Groot, J., Van Hoek, M. & Hoedemaekers, C. 2015. Decision making on organ donation: the dilemmas of relatives of potential brain dead donors. *BMC Medical Ethics*, 16:a64. https://doi.org/10.1186/s12910-015-0057-1

Department for Education England. 2019. *Children looked after in England (including adoption), year ending 31 March 2019*. London: Department for Education.

Editorial. 2017. Organ donation: opting in or out. *British Journal of General Practice*, 68(667):62-63. https://doi.org/10.3399/bjgp18X694445

Encyclopaedia Britannica. n.d. The strange, grisly history of the first blood transfusion. https://bit.ly/3AELEx6

Gratwohl, A., Pasquini, M.C. & Aljurf, M. 2015. One million haemopoietic stem-cell transplants: a retrospective observational study. *The Lancet Haematology*, 2:e91-e100. https://doi.org/10.1016/S2352-3026(15)00028-9

Groth, C.G. 1972. Landmarks in clinical renal transplantation. *Surgery, Gynecology & Obstetrics*, 134(2):323-328.

Hardy, J.D., Kurrus, F.D., Chavez, C.M., Neely, W.A., Eraslan, S., Turner, M.D., Fabian, L.W. & Labecki, T.D. 1964. Heart transplantation in man: developmental studies and report of a case. *JAMA*, 188:1132-1140. https://doi.org/10.1001/jama.1964.03060390034008

https://doi.org/10.52779/9781991201959/05

Hu, W., Lu, J., Zhang, L., Wu, W., Nie, H., Zhu, Y., Deng, Z., Zhao, Y., Sheng, W., Chao, Q., Qiu, X., Yang, J. & Bai, Y. 2006. A preliminary report of penile transplantation. *European Urology*, 50(4):851-853. https://doi.org/10.1016/j.eururo.2006.07.026

Hwang, N.S., Varghese, S. & Elisseeff, J. 2008. Controlled differentiation of stem cells. *Advanced Drug Delivery Reviews*, 60(2):199-214. https://doi.org/10.1016/j.addr.2007.08.036

Jones, B.P., Saso, S. & Bracewell-Milnes, T. 2019. Human uterine transplantation: a review of outcomes from the first 45 cases. *BJOG*, 126(11):1310-1319. https://doi.org/10.1111/1471-0528.15863

Jouan, A. 2016. "Décès d'Isabelle Dinoire, première greffée du visage" [Death of Isabelle Dinoire, first facial grafted]. *Le Figaro (in French)*. [Accessed 6 September 2016].

Kanagasundram, S. & Amini, F. 2018. Late complications of allogenic stem cells transplantation in leukaemia. *Tissue Engineering and Regenerative Medicine*, 16(1):1-9. https://doi.org/10.1007/s13770-018-0157-3

Kootstra, G., Daeman, J.H. & Oomen, A.P. 1995. Categories of non-heart-beating donors. *Transplantation Proceedings*, 27(5):2893-2894. https://pubmed.ncbi.nlm.nih.gov/7482956/

Mohamed, R.Y., Verheijde, J.L. & McGregor, J. 2007. "Non-heart-beating" or "cardiac death" organ donation: why we should. *Journal of Hospital Medicine*, 2(5):324-334. https://doi.org/10.1002/jhm.204

O'Donovan, L., Williams, N.J. & Wilkinson, S. 2019. Ethical and policy issues raised by uterus transplants. *British Medical Bulletin*, 131(1):19-28. https://doi.org/10.1093/bmb/ldz022

Perkins, K.M., Boulet, S.L., Jamieson, D.J. & Kissin, D.M. 2016. Trends and outcomes of gestational surrogacy in the United States. *Fertilility & Sterility*, 106:435-42.e432. https://doi.org/10.1016/j.fertnstert.2016.03.050

Reardon, S. 2022. First pig-to-human heart transplant: what can scientists learn? *Nature*, 601:305-306. https://doi.org/10.1038/d41586-022-00111-9

Reemtsma, K., Mccracken, B.H., Schlegel, J.U., Pearl, M.A., Pearce, C.W., Dewitt, C.W., Smith, P.E., Hewitt, R.L., Flinner, R.L. & Creech, O. 1964. Renal heterotransplantation In Man. *Annals of surgery*, 160(3):384-410.

Ridley, S., Bonner, S., Bray, K., Falvey, S., Mackay, J. & Manara, A. 2005. The Intensive Care Society's working group on organ and tissue donation. UK guidance for non-heart-beating donation. *British Journal of Anaesthesia*, 95(5):592-595. https://doi.org/10.1093/bja/aei235

Rifkin, W.J., David, J.A., Plana, N.M., Kantar, R.S., Diaz-Siso, J.R., Gelb, B.E., Ceradini, D.J. & Rodriguez, E.D. 2018. Achievements and challenges in facial transplantation. *Annals of Surgery*, 268(2):260-270. https://doi.org/10.1097/SLA.0000000000002723

Rivera, R., Yacobson, I. & Grimes, D.1999. The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. *American Journal of Obstetrics & Gynecology*, 81:1263. https://doi.org/10.1016/S0002-9378(99)70120-1

Sarbey, B. 2016. Definitions of death: brain death and what matters in a person. *Journal of Law and the Biosciences*, 3(3):743-752. https://doi.org/10.1093/jlb/lsw054

Siminoff, L.A., Agyemang, A.A. & Traino, H.M. 2013. Consent to organ donation: a review. *Progress in Transplantation*, 23(1):99-104. https://doi.org/10.7182/pit2013801

Snyder, E.A. & Loring, J.F. 2006. Beyond fraud: stem-cell research continues. *The New England Journal of Medicine*, 354:321-324. https://doi.org/10.1056/NEJMp058323

South African National Health Act. 2008. Regulations regarding the general control of human bodies, tissue and organs for transplantation. *Government Gazette*, 7 March:16.

https://doi.org/10.52779/9781991201959/05

Tachibana, M., Amato, P., Sparman, M., Gutierrez, N.M., Tippner-Hedges, R., Ma, H., Kang, E., Fulati, A., Lee, H.S., Sritanaudomchai, H., Masterson, K., Larson, J., Eaton, D., Sadler-Fredd, K., Battaglia, D., Lee, D., Wu, D., Jensen, J., Patton, P., Gokhale, S. & Mitalipov, S. 2013. Human embryonic stem cells derived by somatic cell nuclear transfer. *Cell*, 153(6):1228-1238. https://doi.org/10.1016/j.cell.2013.05.006

Van der Merwe, A., Graewe, F., Zuhlke, A., Barsdorf, N., Zarrabi, A., Viljoen, J.T., Ackermann, N.W., Spies, P.V., Opondo, D., Al-Qaoud, T., Bezuidenhout, K., Nel, J.D., Bailey, B. & Moosa, M.R. 2017. Penile allotransplantation for penis amputation following ritual. *The Lancet*, 390(10099): 1038-1047. https://doi.org/10.1016/S0140-6736(17)31807-X

Vazin, T. & Freed, W.J. 2010. Human embryonic stem cells: derivation, culture, and differentiation: a review. *Restorative Neurology and Neuroscience*, 28(4):589-603. https://doi.org/10.3233/RNN-2010-0543

Zhang, L.C., Zhao, Y.B. & Hu, W.L. 2010. Ethical issues in penile transplantation. *Asian Journal of Andrology*, 12(6):795-800. https://doi.org/10.1038/aja.2010.88

https://doi.org/10.52779/9781991201959/05