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Pig-to-human xenotransplantation: Overcoming ethical obstacles

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Interest in animal-to-human transplantation has significantly increased owing to the limits placed on successful human-to-human organ transplantation by chronic scarcities of donated human organs, and transplant rejection. Extracting and transplanting organs from pigs is a promising solution to the current, increasing, global crisis of human organ scarcity, and would provide a vast supply of organs, which could be obtained quickly and selectively. Although potential harms of pig-to-human xenotransplantation exist, such as cross-species infection, transplant rejection, psychological harm, risks of wear and tear and threats to altruism, these harms may be mitigated through appropriate strategies. We address the objection that xenotransplantation is unnatural. We respond that the sense in which xenotransplantation is unnatural is unclear, and moreover, does not demonstrate that it is wrong. Overall, we claim that the benefits of pig-to-human xenotransplantation are likely to outweigh the harms, if appropriate steps are taken. Genetically modified pigs offer hope for a vast supply of organs for transplant in patients, along with a potentially avoidable risk of transplant rejection and disease transmission.

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Humans have long been captivated by the possibility of merging physical features of animals and humans. This is evident in Greek, Roman and Egyptian mythology, in which human-animal hybrids are deeply entrenched.[1] Xenotransplantation, which is the transplantation of organs, tissues or clusters of specialised cells from one species to another, may seem like a modern extension of this ancient mythology.[2]

Interest in animal-to-human transplantation (xenografts) has significantly increased in the last few decades, owing to the limitations on successful human-to-human organ transplantation (allografts) resulting from chronic scarcities of donated human organs, and transplant rejection.[3] Pig organs are of particular interest, and hold enormous potential to mitigate the rising demand for transplantable human organs, by creating a new and vast supply of organs for human transplantation, thereby potentially resolving the crisis of human organ scarcity.[3]

Still, xenotransplantation raises several ethical issues. While the ethical and regulatory aspects are much discussed in international contexts, there is little work that considers the South African (SA) context.[4] This is problematic, since in SA there is currently no direct legislation or regulation addressing xenotransplantation.[4] To inform potential regulation in SA, we address the ethics of fatally extracting pig organs for transplantation in humans, and argue that: (*i*) the benefits of the intervention are likely to outweigh the harms, provided harm mitigation strategies to be discussed are employed; and (*ii*) that the perceived unnaturalness of xenotransplantation ought not be considered an obstacle to its morality.

Before proceeding, it is important to clarify our scope in three respects. First, our focus is on pig-to-human organ transplantation, rather than xenograft cell and tissue transplantation. This is because the donation of organs appears likely to raise more significant ethical and emotional concerns. Second, our focus on pigs in particular for xenotransplantation is justified by the fact that this is the type of animal source about which there is the most scientific knowledge. The scientific basis for our claim may differ in other animal species. A third clarification of scope is that we do not address objections to xenotransplantation based on the morality of killing pigs. While these objections are important, the current focus is on rebutting objections stemming from the potential harms to human society, and concerns that xenotransplantation is unnatural. We hope to deal with objections related to the moral status of pigs in another publication.

In the following section we provide background on medical research on xenotransplantation. Subsequently, we draw on empirical evidence concerning the potential harms and benefits of pigs in human xenotransplantation, and claim that great potential benefits justify xenotransplantation, provided that the harm mitigation techniques we discuss are employed. Thereafter, we consider the objection that xenotransplantation is 'unnatural', and claim that the objection fails due to the indistinctness of the term natural, and because the (un)naturalness of a practice or intervention is an unreliable guide to its morality or goodness. We conclude by discussing some implications for the SA context.

Context

A few forms of xenotransplantation are already practised, such as replacing human heart valves with pig heart valves to treat heart valve disease.[5] However, the status quo of pig organ transplantation

is experimental, and xenotransplantation instead often involves non-human primates as the standard choice of research subjects.[6] Pig-to-human organ transplants have not been executed, but are likely to be feasible, not least because of the advances in genome editing technology, such as CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats (CRISPR) CRISPR-associated protein-9).[7] Using this genome editing technology, attempts at the first clinical trial involving a pig-to-human organ transplant will soon take place.[7] This means that ethical analysis of the issue is timely.

Potential benefits

In this section we discuss the potential benefits of pig-to-human xenotransplantation. We claim that since there are clear benefits, and it is feasible that the process will avoid major harms to humans, pig-to-human xenotransplantation is in keeping with the ethical principles of beneficence and non-maleficence.[8]

Benefits of using pigs

There are several reasons why the pig is regarded as the ideal candidate from which to source organs. Firstly, pig organs are similar to human organs. For example, the pig heart and human heart have similar cardiac output, stroke volume, mean arterial pressure, heart rate and myocardial blood flow.[9] Likewise, the pig kidney is similar to the human kidney in its maximum concentration ability and glomerular filtration rate.[9] Serum electrolytes, creatinine and urea nitrogen are also comparable, and the pig liver is capable of producing coagulation factors that maintain an appropriate coagulation profile.[9]

The length of pregnancy for a pig is approximately 114 days, and the animals produce litters of 5 - 12 at a time, making the build-up of a herd relatively rapid.[10] Pigs also reach reproductive maturity within 4 - 8 months of birth, and their organs are of adequate size for transplanting in humans, when fully developed.[10]

Another benefit is that pigs are easy and relatively inexpensive to maintain, and can be bred and housed under clean conditions, providing a source for infection-free porcine organs, which could also be genetically modified to further eliminate viruses.[5,10] However, it is important to note that although genetic modification raises its own ethical issues, it is still widely practised, and a complete examination of these issues is beyond our current scope.

Additionally, sourcing organs from pigs would bring about noticeably less public controversy than another similar animal species, since large numbers of pigs have traditionally been slaughtered for centuries.[10] Sourcing organs from non-human primates would result in heavier objections from society, since non-human primates are phylogenetically similar to humans, which entails a greater risk of cross-species infection, and they possess the capacity for emotional depth and altruistic behaviour.[11,12]

General benefits of xenotransplantation

Extracting and transplanting organs from pigs is a promising solution to the current, increasing, universal crisis of human organ scarcity, and could provide a vast supply of organs, which could be obtained quickly and selectively.[9] This could avoid the several adverse effects that brain death has on donor organs.[9] There would be significant reductions in the overall number of patients on waiting lists, and an improvement in patient survival rates, as transplants could be performed as soon as required.[11]

The need for a set of inclusion and exclusion criteria for fair organ allocation would potentially be dissolved, because transplantation procedures could be performed on many 'borderline' candidates, such as individuals with severe cardiomyopathy, who might otherwise be declined.[11] Pig-to-human xenotransplantation is also envisioned as a bridge for patients awaiting a human organ (allograft), because a xenograft organ could be transplanted to the patient to sustain their life until an allograft organ becomes available.[11] Thus organs could be allocated equally and justly to all transplant patients, reducing the potential obstacle of a patient's inability to settle the financial costs of the surgical procedure.[11]

The practice of pig-to-human xenotransplantation may potentially reduce the motivation to practise illegal organ harvesting, and the extraction of organs from executed prisoners without obtaining full informed consent from their families.[11,13]

Complications such as pain, disfigurement and disability in living organ donors will potentially also be alleviated, along with the possibility of sidestepping some cultural barriers that oppose cadaveric organ donation owing to the traditional belief that a body should be complete upon cremation, such as in Japanese culture.[9]

The abovementioned benefits of pig-to-human xenotransplantation are significant, and it would promote saving human lives. However, benefits are often accompanied by potential risks. In the following subsection, we discuss potential harms of pig-to-human xenotransplantation, and consider how these harms may be mitigated.

Potential harms and mitigation approaches

Although it is impossible to safeguard against all possible harms, we claim that most can be mitigated. The subsection below gives an account of potential harms and possible approaches to mitigate each harm, along with the potential success of some approaches.

Zoonosis

The risk of zoonosis is the most scientifically worrisome of all the objections. Couched in ethical terms, it holds that it is unethical for an individual to benefit from a xenograft organ at the cost of putting the public at risk for cross-species infection.[14] Given that transmittable microorganisms can be benign in one species but fatal when introduced into a different one, the potential transmission of porcine endogenous retroviruses (PERVs) is of serious concern. PERVs are dormant in the genetic material of all pigs, and may become active in humans.[15] Consequently, the organ recipient is at risk for infection with PERVs, and also has the potential to expose the surrounding population to this virus, such as friends and family, healthcare professional and other members of society.[15]

Although the threat posed by zoonosis should not be underestimated, the potential risk for zoonotic infection with PERVs can be diminished or eliminated through two significant strategies. Firstly, to reduce the risk of PERV infection in humans, pigs can be tested for retrovirus levels, to ensure that organs are only harvested from pigs with low levels of PERVs.[5] The herd can also be housed and bred under ideal, sterile and isolated conditions, as

well as routinely and systematically monitored and screened for any infectious agents.[5] This would allow for the elimination of pathogens through the cautious selection of pigs.[5] Additionally, Niu *et al*.[7] have suggested establishing national and local registries for xenograft recipients. Doing so would significantly assist in the monitoring and surveillance of recipients and their social contacts, although this type of surveillance may also raise ethical issues.[7]

A second potential mitigation strategy is that pigs could be genetically engineered through the use of genome editing techniques, such as CRISPR-Cas9.[7] This technology allows for simultaneous alterations of various parts of the genome, which facilitates the removal of the PERV encoding sequences from the genome of the pig.[7] Accordingly, research conducted by Niu *et al*.[7] resulted in the successful inactivation of all PERVs in a porcine primary cell line, thereby producing PERV-free pigs, which may entirely eliminate the risk for cross-species infection.

It is also worth pointing out that the risk of PERV transmission is lower than sometimes presumed – a factor that contributed to the lifting of the global ban on xenotransplantation in some countries.[5] Indeed, recombinant porcine factor VIII (FVIII) has been used to treat patients with a severe inherent bleeding disorder (haemophilia) through intravenous injection with pig factors from purified pig plasma.[5] Although the pig product still contained the proviruses (PERVs), it did not infect patients, suggesting that PERVs are specific to pigs.[5] Therefore it appears that the potential risk for infection with PERVs is less significant than sometimes thought.

Despite this, the two highly successful mitigation strategies discussed above have been developed to ensure that this potentially low risk for infection is significantly diminished or eliminated. The next subsection addresses another objection, regarding the risk of transplant rejection.

Transplant rejection

A further objection to pig-to-human xenotransplantation holds that it is unethical to perform xenotransplantation because it may result in the death of the recipient due to the rejection of the xenograft organ from the recipient's immune system.[9] This objection is supported by the molecular incompatibilities that exist between pigs and humans, owing to the phylogenetic distance between the two species.[5] Consequently, a series of immune complications and potential transplant rejection may follow a xenograft transplant, as the recipient's immune system recognises the transplanted organ as foreign and rejects it.[5,9] However, mitigation strategies have been developed to prevent the potential risk of transplant rejection.

One approach is to suppress the recipient's immune system with immunosuppressant drugs. However, these drugs can be detrimental to the wellbeing of the recipient, as they are accompanied by adverse effects and may compromise the recipient's ability to fight off infection(s).[16]

Alternatively, genome modifications in pigs may diminish the cross-species immune barrier through preventing the recipient's immune system from recognising the xenograft as foreign, thereby inhibiting the transplant rejection processes.[16] Genetically modified pigs can be obtained through several techniques, namely pronuclear and cytoplasmic microinjection, somatic cell nuclear transfer and viral transduction of DNA.[5]

Additionally, 'tolerance approaches' are another available strategy for mitigating the potential risk of transplant rejection. These approaches aim to attain immunological tolerance in the recipient's body through co-transplanting an organ along with the source pig's bone marrow.[17] The recipient is initially placed on immunosuppressant drugs to avoid the bone marrow being rejected, followed by gradually reducing the dosage until complete withdrawal of the drug is reached.[17] The recipient's immune system will ultimately recognise the porcine immune cells as its own, and will not attack or reject the xenograft organ.[17]

The success of this approach has been demonstrated in xenotransplantation involving non-human primates, where minimal or no immunosuppressive drugs were used because immunological tolerance was achieved.[17] As another example in humans, several patients who underwent an allograft (human-to-human) kidney transplant at the Massachusetts General Hospital have still not taken immunosuppressive drugs several years post surgery because of the immunological tolerance that was achieved through the tolerance approach.[17] Other tolerance approaches are also currently being researched.[17]

It is also possible to combine the above approaches. The combination of genetically modified pigs, the tolerance approach and some immunosuppressive drugs may effectively reduce or eliminate the risk of transplant rejection.[6] While the risks of zoonosis and transplant rejection can be eliminated, the potential risk of psychological harm to recipients also exists. The next subsection addresses this issue.

Psychological harm

It could be argued that the xenograft organ recipient might lose his/her sense of identity, and feel less human after the transplantation.[18] Allograft organ recipients often report experiencing complex emotions around having received another person's organ, and the complexity of negative emotions may be magnified in recipients of xenograft organs.[18] Some organs are more integrally connected to one's sense of self than others: for example, a heart transplant is more likely to evoke questions of identity, because it is traditionally believed to harbour one's feelings and character.[18] Consequently, xenograft recipients may experience negative psychosocial impacts because of potential harm to their personal identities.[18]

One strategy in response to this is to attempt to reconcile the self-perception and body image of xenograft recipients through instigating pre- and post-surgical counselling.[18] This would positively assist recipients in accepting the changes in their circumstances.[18]

It is also important to recognise that the identity of the individual would in fact remain unchanged, and that the challenge is to overcome an emotional rejection of the alteration to the body.[18] In this case, the media could be crucial in attempting to normalise or accept the concept of hybridity to the public.[18] Below, further potential harms are discussed.

Wear and tear

Additionally, there is also a risk of xenograft organs wearing out or failing prematurely, because pigs typically have a shorter lifespan than humans, that is, 10 - 15 years.[19,20] This means that their tissues

age at a quicker rate than human tissues.[19] Knowledge on the longevity of xenograft organs in humans is deficient.[20] However, it is important to recognise that the use of porcine organs would become more common and probably reduce the cost of organ donation, meaning that, assuming they were required, later additional surgeries would be available and affordable.

Altruism

Another potential harm of xenotransplantation may include the gradual disappearance of altruistic human organ donations. Altruism is an important value that allows society to flourish.[11] Moreover, the decline of altruistic human donations could mean that individuals opposing xenotransplantation may be negatively affected should they require an organ transplant, because allograft organs may no longer be available.[11] However, donation of one's organs, while a worthy sacrifice, is by no means the only possible outlet for altruism, so there is no need to posit altruism's general decline. Moreover, while a reduction in donations is likely, there is no reason to think that there will be insufficient numbers available to accommodate the population group opposing pig-to-human xenotransplantation.[11]

In this section we have examined the benefits and potential harms of pig-to-human xenotransplantation. It is clear that the intervention holds promise in terms of resolving the global crisis of human organ scarcity. Moreover, the potential harms can be effectively mitigated.[5] Pig-to-human transplantation could improve human lives, and would be relatively safe to execute.[5]

Natural v. unnatural

This section examines the objection that xenotransplantation is unnatural and, consequently, wrong.[21] According to this objection, it is wrong for humans to carry animal organs in their bodies because it meddles with the order and structure of nature.[21] This is sometimes referred to as an 'appeal to nature.'[21] A related argument is that interfering with the order and structure of nature involves 'playing God', because the human role is shifting from that of creation to creator.[11] In this way, pig-to-human xenotransplantation is seen to contravene the relationship between humans and nature, or between humans and God.[11] In response to this, we claim that the indistinct meaning of the term 'natural' prevents appropriately classifying xenotransplantation as unnatural.[22] Moreover, we claim that the assumed moral parity between what is good and what is natural is unjustified.[22]

Is xenotransplantation 'unnatural'?

Caution must be taken when rejecting pig-to-human xenotransplantation purely on the grounds that it is 'unnatural', because that ground for rejection can merge imperceptibly with the 'yuck-factor'.[23] The yuck-factor is the intuitive repulsion one feels towards something, which may lead one to consider something to be wrong based on these feelings of repugnance.[23] The relationship between disgust and morality is contested in an extensive literature.[24] However, it is commonly thought that the idea of what constitutes naturalness is often clouded by irrational evolutionary 'yuck' responses.[25] It is thus important for proponents of this appeal to nature to clarify their terms, since what is recognised or regarded as unnatural is rather unclear and seldom specified.

It is important to note that there is a prevalent societal tendency to base moral judgements on an inference that something is 'unnatural,' for example, incest and cannibalism. However, again, it is not clear that these are unnatural, since both occur in nature. Moreover, a better explanation of the 'wrongness' of such activities, to the extent they are wrong, is more likely to stem from their harmful consequences, rather than what is generally a non-rational judgement or intuition about their 'unnaturalness.'

Similarly, Bisong[21] claims that society tends to perceive xenotransplantation with some disquiet, which is why it is often rejected on the basis that it is unnatural.[21] He also claims that 'it is this same line of reasoning that leads to a large-scale disquiet regarding homosexuality and other areas of medical science such as assisted conception and reproduction, cloning and most other forms of genetic engineering.' Bisong claims that the perception of what is 'natural' tends to be driven by pre-existing moral beliefs, superimposed on vague conceptions, rather than clear definitions, of what is natural, leading to conclusions about what is right and wrong.[21]

The suggestion, then, is that there is similarly no clear, unambiguous sense in which we can say that xenotransplantation is 'unnatural' that does not have counterintuitive implications. Moreover, if Bisong is correct, then judgements about the unnaturalness of xenotransplantation are often misinformed, instead being based on non-rational intuitions about what is wrong. It is therefore unclear both that xenotransplantation is unnatural, and that its purported unnaturalness is the reason that it is regarded as unethical.

Natural is not always good

A key problem with the appeal to nature is that it appears to entail that everything natural is good/right, and everything unnatural is bad/wrong.[22] To better understand the problem with this, consider two intuitive understandings of the natural/ unnatural divide: (*i*) unnatural things or elements are those that are made by humans and involve interventions in nature; and (*ii*) that which is natural is that which occurs in nature. Even allowing that these are the justified reasons or genuine motivations for objecting to xenotransplantation (which we have denied above), it should be clear that counterintuitive implications follow from identifying what is natural with what is good, and vice versa.

For instance, these definitions entail that natural disasters and diseases are also good, because both occur in nature and involve no human interventions.[22] In this view, all attempts to prevent natural disasters or administer medicine might be conceived as unnatural, and therefore unethical. Clearly this conclusion should be rejected.

Therefore, even if one considers that the issue of indistinctness can be resolved such that there is a clear basis for saying that xenotransplantation is unnatural, we should nonetheless reject the claim that what is natural is good/right. The appeal-to-nature objection to xenotransplantation should be rejected. Below, we conclude by discussing the implications of the arguments in this article, and some considerations to guide legislation and regulations regarding xenotransplantation.

Conclusion

Pig-to-human xenotransplantation holds high potential for resolving the growing crisis of human organ scarcity.[3] Genetically modified

pigs offer hope for a vast supply of organs for transplant in human patients, along with a minimal risk of transplant rejection and disease transmission.[5,10] Yet these benefits are not without potential risks and ethical concerns, which themselves provide a strong motivation to be wary. However, we have argued that potential harms, such as zoonosis, transplant rejection and psychological harm, can be mitigated effectively, and that xenotransplantation offers the opportunity to improve or save human lives. Furthermore, the objection that xenotransplantation is unnatural fails, since there is no clear sense in which xenotransplantation is unnatural, and even if there were, this would not demonstrate that it was wrong. These objections thus fail to show that it is ethically unjustifiable to fatally extract pig organs for use in humans to save human lives.[6]

In concluding, it is important to re-emphasise that there is currently no direct SA legislation or regulation addressing xenotransplantation.[4] In introducing such law and regulation in a SA context, it will be important to find culturally sensitive ways to overcome stigma associated with the use of pigs' organs, as well as to take into account the harm mitigation strategies considered above.

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