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"The Relevant History and Medical and Ethical Future Viability of Xenotransplantation"

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Table of Contents

Preface

In order to tackle the medical ethical issues within the research field of xenotransplantation, we must study: (1) the relevant history of xenotransplantation, (2) the true medical viability of xenotransplantation and the possibilities of operative risk, (3) The ethical dilemmas within xenotransplantation, especially through a multicultural lense, (4) the arguments against xenotransplantation, (5) the arguments for xenotransplantation and then we are obligated, as medical ethicists to discuss what can be done within the field. The aim of this paper is to build a comprehensive model of the current field of xenotransplantation as well as its history, in order to better understand the moral and ethical challenges facing those working in the field today.

Relevant History of Xenotransplantation

What does it mean to perform the first successful xenotransplantation in human history? This question is difficult to answer as there are several people throughout recent history that claim they performed the 'first successful xenotransplantation'. In preparation for the ethical discourse of xenotransplantation we must first examine the relevant history of xenotransplantation. First, to define xenotransplantation simply, "it is the process of transplanting or infusing live cells, organs, or tissues from an animal source into a human recipient" (Brinson 1).

Transplantation is considered one of the most challenging sectors of modern medicine. There are more patients awaiting a transplant than available organs, the wait list is growing exponentially every year (Berki 1). Xenotransplantation has long been an appealing possible solution for the human organ shortage but until recent breakthroughs in modern medicine was not considered a viable option. The ideas that existed in the form of what we now refer to as xenotransplantation date back to 1667, when a French doctor by the name of Jean-Baptiste

Denys tapped the veins of farm animals to perform human blood transfusions (Berki 1). “His first patient, a 15-year-old boy, miraculously survived the procedure likely due to the small amount of sheep blood that he received and that allowed him to withstand the allergic reaction. The practice, however, was soon banned as two further patients of Denys died” (Berky 1). Skin xenografts became popular in the 19th century and surgeons had begun experimentation to use many different species as donors, including rabbits, dogs, and even pigeons. Medical historians now believe that none of the grafts became permanent. Likely, they simply aided wound healing by covering the skin and providing protection to it (Berki 1).

“In the beginning of the 20th century, French surgeon Alexis Carrel developed a surgical technique (anastomosing/connecting blood vessels) that enabled the first succesful organ transplantation: Joseph E. Murray and his colleagues at the Brigham Hospital, Boston, successfully transplanted a kidney between two identical twin sisters in 1954” (Berki 1). Not long after, the limited availability of donor organs raised an interest in animal sources. “Professor Keith Reemtsman from Tulane University, Louisiana hypothesized that primate kidneys could function in human recipients. He selected the chimpanzee as a potential donor because of the species’ close evolutionary relationship to humans" (Berki 1). Reemtsman carried out 13 chimpanzee-to-human kidney transplants in 1963-1964 but none of the patients survived more than 9 months, in fact almost all of them died less than two weeks after the surgery. Dr. Thomas E. Starzl, another notable physician, performed liver transplants between chimpanzees and numerous young patients with the same devastating outcome, regardless of the advent of cyclosporine, the first immunosupressant drug invented and used for operation (Berki 1). “In the late 1980s, a pioneering heart transplant surgeon Dr. David Cooper began to argue that monkeys are not the best donors for humans. His most important argument was in regards to the size of the

organs - he thought that the heart of a monkey is simply not big enough for a human adult while pigs, on the other hand, could be a more suitable alternative" (Berki 1). Unfortunately all of Dr. Coopers' attempts to transplant organs from pigs to humans were unsuccessful. However, Dr. Coopers' lab made a breakthrough a decade later, in the late 1990s. "The Cooper lab identified the sugar alpha-1, 3-galactose on the surface of porcine cells as the main trigger for the human immune system. Soon the first genetically modified, alpha 1,3-galactosyltransferase gene-knockout pigs appeared and biotech companies began to invest a vast amount of money into developing an animal whose organs would be satisfactory for xenotransplantation" (Berki 1). Notably, Genzyme and PPL Therapeutics (two of the companies heavily involved with the creation of Dolly the sheep) were planning investments into the genetic engineering of pigs as viable alternatives to regular organ transplantation.

As this development was ongoing scientists reported a shocking discovery: the existence of PERV or Porcine Endogenous Retrovirus, a virus that could infect human cells and unleash a deadly human epidemic. Around 2001 when this discovery occurred there were also numerous worldwide protests of animal-rights activists, and a majority of all biotech companies chose to terminate their experiments and close their labs (Berkin 1).

Most recently, three major breakthroughs have taken place within the field of xenotransplantation research, and the community is acting as though an exciting fire has been reignited. First, throughout the 2010s the group of Prof. Muhammad Mohiuddin from the National Heart Lung and Blood Institute took further steps and successfully inserted two human genes into the pig genome: one that protects cells from an attack by the complement system, and another that prevents harmful coagulation. These are the human complement regulatory gene CD46 and the human thrombomodulin genes (Berkin, 1). This will allow organs from pigs

transplanted into humans to live longer as the cells will be able to protect themselves. Second, “In August of 2017, researchers from the George Church and Luhan Yang lab at Harvard announced quite a breakthrough in xenotransplantation: they had used the CRISPR-cas9 system, a cutting-edge gene-editing technique, to inactivate 62 PERV genes in pig cells. From these fetal cells they cloned embryos, and out of the 37 piglets born, none of them showed any genetic trace of the PERV virus” (Berki 1).

The third, most recent breakthrough in xenotransplantation is a man by the name of David Bennett, Sr., the first person to have his heart replaced with that of a genetically modified pig. On Friday, January 7th, 2022 Mr. Bennett underwent surgery at the University of Maryland Medical Center after the center recieved emergency approval from the US Food and Drug Administration under the Compassionate Care Act (Williams, 1). Additionally, “Doctors at the University of Maryland Medical Center were granted a special dispensation by the US medical regulator to carry out the procedure, on the basis that Mr Bennett - who was ineligible for a human heart transplant would otherwise have died” (BBC 1). The center was the first in decades to attempt the transplantation of a heart into a human from another species and it was the first operation to ever use a heart from a genetically engineered pig to avoid rejection by the human immune system. The pig that provided Bennett’s new heart had four genes ‘knocked out’ or inactivated and six human genes added, all with the goal of preventing the human immune system rejection. An additional gene was knocked out to prevent the heart from continuing to grow post transplantation (Williams 1). Mr. Bennett had terminal heart disease and knew the risks attached to the surgery, acknowledging before the procedure it was a ‘shot in the dark’ (BBC, 1). Unfortunately, Mr. Bennett passed away just two months after the surgery.

The Elephant in the Room - True Medical Viability & Operative Risk

The true medical viability is of major concern to the medical and research communities as of late. Up until last year researchers, physicians and the people developing the cutting edge of xenotransplantation research and technology didn't yet believe xenotransplantation was fully viable - the rhetoric has been one of 'proceed with caution'. The community believed more research needed to be done but with the case of David Bennett, Sr. being presented, it was an opportunity for those who wished to push our developed methods and technologies to the limit, to do so in the hopes that we may gain something new. Although David Bennett, Sr. lived up to two months after his groundbreaking surgery this does not necessarily mean we are yet at a place of true medical viability. Before true medical viability can be reached there are two important problems that must be completely solved: rejection of transplanted organs by the recipient's body, and risk factors related to diseases that jump species lines (Lee 1). These are the exact same major problems that have been plaguing xenotransplantation since its conception. "In the case of all organ transplants, the immune system of the recipient identifies the transplanted organ as a foreign invader and attacks it. In order to prevent rejection of the transplanted organ, cyclosporine and other drugs must be administered to the recipients of transplanted organs in order to partially suppress their immune systems. The severity of the rejection response depends, in part, on tissue match. The better the tissue match, the less severe the rejection response" (Lee 1). Xenotrasplantation struggles with the differences in tissue matches because pig to human or chimpanzee to human tissue matchs are not the same as human to human tissue matches demonstrating the rejection response of the human immune system as being even more severe. This requires more aggressive efforts when it comes to the development and use of immunosuppressive drugs which then in turn leaves the recipient with little to no protection

against infectious diseases. An important side note here: those very same infectious diseases that the recipient has no protection from could come from the hospital environment during recovery or if it is a disease that has the capability of jumping species line, the newly transplanted organ. “Efforts are being made to modify the genetic characteristics of organs to be transplanted to make them less likely to be rejected by the recipient. The research in this area, however, is still in its early stages” (Lee 1). To expand upon this further and in regards to the most current available data what happens almost immediately after a xenotransplantation is known as hyperacute rejection and it is the immune systems’ response to non human organ transplantation - in a matter of just a few minutes the body mobilizes an attack force to completely destroy the organ (BIO 1). Rather than focus on new methods of immunosuppressive drugs, one technology being developed to overcome hyperacute rejection is the breeding of transgenic pigs. “These genetically-altered pigs express specific human proteins that make it more difficult for the human immune system to identify the porcine organ as belonging to a different species. A transgenic pig is bred by injecting a small amount of DNA mimicking a human gene sequence into a fertilized pig egg and then implanting that egg into a sow leading to the pig’s birth. Recent studies have shown this technique has addressed hyperacute rejection in nonhuman primates that received organs from transgenic pigs” (BIO 1). The latest nonconcrete proposals have discussed newer forms of cloning technology (similar to that used in the creation of Dolly the sheep) that show promise for further enhancing the immunocompatibility of pig organs by eliminating the pig-gene products that cause hyperacute rejection. In theory these developments should mean that once transplanted, animal organs could be treated in the same way as human organs, with the use of standard immunosuppressive regimens, but these developments are in very early stages (BIO 1). The second major surgical concern is the possibility that pig diseases might jump

species lines and pose serious risks to human health and well-being. There are several examples of deadly diseases that have jumped species lines with devastating consequences for humans. COVID-19, caused by the novel coronavirus that is causing so much concern today, is believed to be one of them. Other examples include AIDS (which is caused by the HIV virus), Ebola, Lyme disease, and bird flu (H5N1.) (Lee 1). Not only is this an ethical issue that warrants serious organized discourse and potential solutions but it's dually something that needs to be addressed from a surgical standpoint. As previously discussed researchers at Harvard in conjunction with researchers from the George Church have indicated that the implimentation of the CRISPR-cas9 gene editing system could inactivate any genes identified as being virus linked. In order for this process to become more widely used within xenotransplantation, a couple of steps need to take place; firstly, in any animal, researchers believe could be possible viable sources of organs, research would need to be completed to identify all possible viruses that could jump species lines, secondly researchers would then have to identify the genes linked to said viruses and inactivate them using the CRISPR-cas9 system. Additionally, it would be of considerable benefit to genetically screen the animals after the gene editing process to ensure no possibility exists of dormant viruses that could jump species lines.

Researching the total medical viability before discussing how to move forward in regards to operative risk is putting the cart before the horse so to speak. "One of the main challenges in surgery has long been to elaborate safe, effective, and technically feasible procedures for the best possible outcomes. Continuous progress in science and technology combined with cumulative experience in the field have refined indications for surgical treatment, prompted standardization of modern surgical techniques, and established comprehensive protocols in perioperative care. The most complex interventions can now be implemented with significantly reduced

intraoperative trauma by using modern instruments and minimally invasive approaches. Surgical procedures became faster and safer, but complications are still prevalent, even in experienced hands" (Shaydakov & Tuma 1). In the United States and around the world one of the largest challenges to surgeons is how to accurately select the best candidates for surgical intervention. “An accuracte prediction of immediate and long-term outcomes becomes an imporant part of an elective procedure that guides preoperatve testing. Failure to identify patients at a high operative risk may be associated with inappropriate postoperative care and significantly increase in-hospital mortality. The selection of patients for surgical treatment is still largely influenced by a surgeon’s personal experience and judgment. However, estimation of an individual risk/benefit ratio for a specific surgical procedure can help to more objectively adopt a nonoperative management strategy or select the best surgical procedure at the most appropriate point of time” (Shaydakov & Tuma 1). Additionally when discussing operative risk, we’re discussing the “cumulative risk of death, development of a new disease or medical condition, or deterioration of a previously existing medical condition that develops in the early or late postoperative period and can be directly associated with surgical treatment.” (Shaydakov & Tuma 1). Anesthesologists and cardiologists each have a developed classification table for assessing a patients’ physical status, their preoperative general health and in-hospital mortality rate. The American Society of Anesthesiology developed their Risk Assesment Model in 1941 and it has been revised heavily throughout the decades and cardiologists use the Revised Cardiac Risk Index Model.

The tools most commonly used in assessing operative risk could be applied to cases of xenotransplantation in the future but the general healthcare system isn’t yet ready. Surgeons including cardiologists and anesthesiolgists will have to first build a moral and ethical framework for why xenotransplantation should be not only a viable option, but one that is readily

available. Next there (in theory) would be years of cost analysis, risk analysis, legal analysis before any hospital systems chose to try and implement the frameworks necessary to provide xenotransplantation, and even then the systems proposed would have to be revised and the 'kinks' would have to be continuously worked out. The sheer amount of possibilities that have to be considered both morally and ethically are so vast and wide that we as a society may still be further away than we think from common xenotransplantation. Not only do we have to master the technical aspects of a new form of surgical intervention (which we haven't done yet), but we have to discuss the morals and ethics under what sets of circumstances should this be viable, operative risk analysis, legal coverage for surgeons and hospitals and even possibilities of new forms of insurance coverage.

Ethical Dilemmas & Xenotransplantation Viewed Through a Multicultural Lense

At this point in our human history, "xenotransplantation, because of the complexity of the medical, ethical and legal issues, will likely remain a controversial issue. If the scientific problems are solved, the decision to proceed with clinical application of this technique will depend on a collective decision guided by ethical, regulatory and legal frameworks established through consensus" (George 1). When thinking about the current state of affairs within xenotransplantation there are many layers of ethics discussions that need to take place; some questions that come to mind are:

"How will researchers know when it is appropriate to move from purely animal studies to clinical activities involving humans?" (Olakanmi & Purdy 1)

"How can we ethically justify the vast amount of money spent on xenotransplantation research given that it will benefit relatively few individuals?" (Olakanmi & Purdy 1)

Will there come a day where we produce animals specifically to genetically engineer them and harvest them for their organs for xenotransplantation? If so, how will we justify doing so?

Are we somehow playing God, or are we perhaps doing the right thing by trying to save and protect as many lives as possible through this new form of surgical intervention?

If xenotransplantation becomes more commonplace, yet we still have more people on the organ donation waitlist than we have organs for, how do we decide who gets a human organ and who gets an animal organ?

These questions weigh very heavily on me as I will oneday be at the forefront of medical research and I wish to only make well reasoned and ethically sound decisions throughout my professional career.

"Unlike allotransplantation, reflections on xenotransplantation are infrequent in theological literature. However, xenotransplantation poses questions specifically concerning ethical and theological aspects that are imperative to address, such as persnal identity between the poles of the body, soul, and mind, the relationship between humans and animals, as well as challenges regarding specific issues of medical and social ethics" (Sautermeister, Mathieu, Bogner 1).

Xenotransplantation Viewed Through a Multicultural Lense

Citing a symposium that took place in Munich, Germany from September 30 until October 2, 2013 titled 'Xenotransplantation - a challenge to the theological ethics' where experts analyzed the implications of xenotransplantation from the perspectives of Christian theological ethics, biblical theology, and systematic theology the results concluded that according to all three perspectives of Christianity, Judaism, and Islam, there are no specifically religious fundamental

and generally binding reasons to prohibit xenotransplantation as a means of treating grave and life-threatening organ insufficiencies (Sautermeister, Mathieu, Bogner 1). Additionally, experts discussed the “metaphorical and religious meaning of the human heart, which may have an impact on the socital acceptability of xenotransplantation, as well as the Christian notion of compassion regarding animals" (Sautermeister, Mathieu, Bogner 1).

Christian Ethics

Unlike allotransplantation (of living and passed human donors), which is widely accepted among theologians, xenotransplantation has found little attention in theological ethics (Sautermeister, Mathieu, Bogner 1). “The Evangelical Church in Germany published a document on xenotransplantation, which is intended to provide assistance in the process of reaching a verdict, not by supplying definitive statements, but rather by pointing to the necessity of an ethical discourse. Some core issues concerning the ethical challenegs arising in the context of xenotransplantation are as follows:

1. The question of the moral status of animals and the transgression of the boundaries between man and animal,
2. The challenge of distributive justice in terms of allocation, and
3. Informed consent, genetic modification of donor animals, as well as psychosocial and sociocultural acceptance of xenotransplantation (Sautermeister, Mathieu, Bogner 1).

The summary of the response of the Evangelical Church in Germany is as follows: ‘Public discourse and societal opinion formation are essential, pre- and postoperative counseling will be crucial, and it should incorporate a spiritual and religious dimension tailored to the patient and

patients family as religious self-conceptions may be affected by xenotransplantation.' (Sautermeister, Mathieu, Bogner 1) **Proceed with Caution.**

Jewish Ethics

"The issue of allotransplantation from dead and living donors as well as xenotransplantation are addressed from the perspective of progressive Judaism. *Pikuach nefesh* - a core principle of Jewish ethics, emphasizes the preservation of human life as superordinate to almost all religious obligations" (Sautermeister, Mathieu, Bogner 1) The necessary precondition for the application of *Pikuach nefesh* principle is the serious and life-threatening manifestation of illness (Sautermeister, Mathieu, Bogner 1). It is without question in the Jewish faith that in the situation where a patient needs an organ donation, not only does this principle allow for it, but it obligates the recipient to consent to the transplantation. The *Kedushat HaChaim* (sanctity of life) hasn't been clarified with respect to the need of xenotransplantation, a very high esteem for human life has always been inherent within Judaism (Sautermeister, Mathieu, Bogner 1). "Although Jewish tradition demands the deceased to be buried entirely, with all body parts, the explanation of donor organs as a contribution to the preservation of human life is not only permitted, but also a mitzvah (moral deed). Once an organ has been transplanted into another human organism, it is no longer viewed as part of the donor, but as part of the recipient's body" (Sautermeister, Mathieu, Bogner 1). A misconception in need of clarification is that a Jewish recipient of a xengenic organ is not viewed as a chimera or a hybrid. Although Judaism does not have any inhibitions of xenotransplantation, there have been some moral and legal arguments brought up within the Jewish tradition that are deemed relevant here. The situation of an organ doner is ethically complicated because of two Jewish moral imperatives: "helping someone desperately in need of a new organ on one hand and being responsible for the preservation of

one's own health on the other hand. According to different Talmudic approaches, destroying a life to save another is not admissible. Modern-day Poskim (legal scholars) have dealt with this problem. The late Ovadja Josef (Sephardi chief rabbi of Israel) argued that a living person is permitted to donate organs or tissue if the potential threat to his own health is exceeded considerably by the acute danger of the potential recipient. There is, however, no compulsion to the fulfillment of this mitzvah. With regard to xenotransplantation specifically and the notion of porcine organs being impure, two basic principles are of major relevance: Hana'a ("pleasure") and the precept that man may use animals for his benefit under certain preconditions. As transplantation cannot be linked with the sentience of Hana'a, implanting animal organs or tissues that are considered impure in terms of kashrut is permitted. Concerning human subject research, the consent to experimentation regarding the benefit of oneself and other patients—under the obligation of pikuach nefesh—can be a mitzvah" (Sautermeister, Mathieu, Bogner 1).

The summary of the response from scholars within Jewish Ethics is this: this situation is quite complex and as technology continues to develop there will be a need for serious legal, ethical and moral debate. **Proceed with Caution.**

Islamic Ethics

The Islamic scholars approached the issue of xenotransplantation with a three pronged approach. Firstly, they studied the Quran and examined closely the perception of animals within the Quran. Several portions of the Quran mention animals as a source of wool, milk, and honey as well as a means of easing man's struggles in agriculture and transport. The Quran interprets animals as a sign of God's mercifulness (Suras 16:79; 6: 6-8)(Sautermeister, Mathieu, Bogner 1). According to Islamic theory, man is expected to justify his actions towards animals. Secondly,

Islamic scholars studied animal ethics; in Islam animals are not viewed as moral subjects, but rather as moral objects and are not ascribed a dignity comparable to the dignity of man. Nevertheless, this implies multiple obligations, such as species-appropriate animal husbandry, that prohibit the exploitation of animals or the infection of avoidable pain (Sautermeister, Mathieu, Bogner 1). It's important to note Islam has no definitive stand on animal testing or the genetic modification of animals. Lastly, Islamic scholars performed a moral evaluation of xenotransplantation. "Three points of reference for the moral evaluation of xenotransplantation from an Islamic point of view are defined:

1. the legitimacy of killing an animal for the sake of explanation,
2. the legitimacy of genetically modifying the organism of an animal,
3. the (primarily dietary) impurity of animals involved." (Sautermeister, Mathieu, Bogner 1).

According to the current Islamic debates and conclusions, man stands at the peak of the hierarchy of creation. The perception of health as something entrusted to man by God creates the obligation to preserve one's own health. With regard to the notion of certain animals being impure, Islamic scholars argue that the distress of potential organ recipients overrules the obligations arising from dietary laws (Sautermeister, Mathieu, Bogner 1).

`From an Islamic perspective, xenotransplantation is justifiable. **Proceed with Caution.**

Pontifical Academy for Life

“The Potifical Academy for Life issued a statement on xenotransplantation that advocates for continued research and clinical trials related to xenotransplantation. It concludes, “the results thus obtained, if unequivocally positive, would constitute the basis for extending the practice of xenotransplantation, making it an accepted surgical therapy.”” (Lee 1). **Proceed with Caution.**

Analysis of Opposing Arguments

There are several general arguments opposing xenotransplantation and they are as follows:

(1) Moral Dilemmas Surrounding the Usage of Animals (Regoli 1)

The main moral question is what are we allowed to do to animals during testing and is it morally and ethically permissible to breed animals specifically for genetic modifications and xenotransplantation purposes? “Animal test recipients may be subject to procedures that cause serious suffering. Some such suffering may be caused by the social context of the research: for example profit-oriented research groups may perceive the demands of humane treatment of animals as obstacles to winning the race, not moral necessities. Even in the best circumstances, some suffering may be unavoidable: surgery causes pain, and drugs can cause a variety of seriously unpleasant symptoms.” (Olakanmi & Purdy 1) Donor animals may also suffer because of the conditions necessary for producing safe organs. Yet another moral question that arises in regards to donor animals is whether they (morally) may be killed for their donations or not? (Olakanmi & Purdy 1)

(2) The Potential Risk of Disease Transmission (Regoli 1)

This problem influences the decision to pursue research and treatment from a private matter to a public one, and it shifts some of the focus to the idea of justice. Generally, we believe that some decisions are personal because the benefits and burdens of those decisions are largely born by the person making the decisions (Olakanmi & Purdy 1). However, when they are not borne by that individual alone, they can become an area of interest to society at large and then it becomes moreso a question of justice. Pursuing xenotransplantation in humans will require researchers to identify viruses that could jump species lines and create a plan of action in order to prevent outbreaks similar to that of COVID-19. This was illustrated very clearly by the COVID-19 Pandemic and how that influenced and changed many aspects of our lives.

(3) Shorter Life Span of the Animal Organ (Regoli 1)

This argument seems to point out the obvious but this is actually a point that researchers haven't yet concerned themselves with. Animals have shorter lifespans than humans, which means that if the success rate of xenotransplantation increases and the survival rate increases, there would most certainly still be a risk of the transplanted organs wearing themselves out, which in turn means that a recipient would need to undergo multiple transplants over their lifetime (Regoli 1).

(4) Risk of Immune System Rejection (Regoli 1)

Hyperacute rejection has been a daunting problem with xenotransplantation in all attempted cases. The biological differences within tissues of different species and a lack of immunosuppresive drug research are largely to blame for the hyperacute rejection. In the current state of research affairs even with the most potent of immunosupressive drugs,

xenotransplantation has not yet proven to be viable as the patients do not live long after the initial surgery due to the immune system rejection.

(5) Informed Consent

The issue of informed consent comes with a couple of questions. Firstly, would potentially viable candidates for xeno consent to the procedure? “Xeno researchers assume that desperate people would gladly take any relevant organ. But studies suggest that might not be true. Some resistance might come from religious beliefs concerning this type of close relationship with non-human creatures. Some resistance might also come from realism concerning the risks and benefits of xeno.” (Olakanmi & Purdy 2)

The second issue is whether candidates for xenotransplantation could ever provide fully informed voluntary consent. “This type of consent is difficult enough to obtain from seriously ill patients for whom any invasive treatment is proposed. The special problems associated with xenotransplantation exacerbate these difficulties.” (Olakanmi & Purdy 2) It’s a very serious situation when a loved one is ill or in pain, fear may prevent them from reasoning through their alternative solutions. “This problem is then compounded by reservations that health care providers may have in fully disclosing the risks inherent in this kind of last-ditch treatments available. These factors often lead patients to consent to treatments that are unlikely to deliver any benefit because they think they have nothing to lose. But patients *can* be made worse off: treatment can impose suffering without any compensating benefit.”(Olakanmi & Purdy 2)

Informed consent for xenotransplantation raises its own new questions. It’s hard to have the same level of surgical precision that we have now, in an entirely new and underdeveloped field of surgery - we can only speculate about what could go wrong and what patients would

experience. Patients and their loved ones would need to be prepared to consent to seriously intrusive and demanding conditions because of the potential risks involved (Olakanmi & Purdy 2). Researchers have proposed potential conditions: lifelong monitoring, using barrier methods of contraception, reporting sexual partners, educating close contacts about potential risk, refraining from childbearing, and accepting quarantine in case of infection. What measurements would the government be willing to take in order to protect the public in case xenotransplantation goes horribly wrong?

A Note on the Moral Dilemmas of Animal Usage

While this is an ethical issue that warrants further discourse this does not seem to be an opposition strong enough to prevent researchers from pursuing xenotransplantation further. Although Christianity, Judaism and Islam all discuss the relationships between man and animal, and in some cases the sanctity of animal life, there are no major explicit religious standards that inhibit animal usage for testing. Scholars within Islam do believe man has to have pure justification for how they treat animals but there has not been an official position taken on animal testing. Additionally, if in the future, xenotransplantation becomes commonplace, what role will hogfarmers play in the raising of genetically modified pigs? How would we regulate the treatment of animals by private companies? Is it even important to do so? These are just some of the questions that require deep and meaningful discussion if we're to ever build a true moral and ethical framework to support xenotransplantation research.

Counter Argument Surrounding the Potential Risk of Disease Transmission

As of 2017, researchers at Harvard identified a method of using the CRISPR-Cas9 gene editing system to deactivate genes linked to viruses within pigs. This method could be

reproduced with pigs or other animals deemed potentially viable for usage in xenotransplantation. In order to prevent a public health crisis researchers would have to identify all viruses that have the possibility of jumping species lines, they would then have to identify the genes linked to said viruses and lastly, during genetic modification researches would have to 'knock out' or inactivate those genes. This has been proven as a viable technique but it does bring about yet another ethical concern. Just because we have the technology available and the knowledge to genetically modify animals for human benefit, should we do so? There is one school of thought that believes the technological capabilities and advancements of the human species will one day fall in the hands of someone who will do great harm. There is another school of thought that believes we should proceed with full speed ahead. The most resounding and appropriate response, given the current state of affairs, is to proceed carefully and with caution.

Potential Response For the Shorter Lifespan of the Animal Organ

This seems to be one of the most difficult arguments against xenotransplantation to which there is no good solution as of yet. Morally, ethically and in regards to surgical technique there is much work to be done. Suppose someone is gravely ill and they will die if they do not have access to a xenotransplanted porcine heart, is it morally acceptable to take them through the surgery (assuming all of the surgical risks are known) only for them to be in the same exact situation just a number of years later? Additionally, if insurance were to cover the enormous cost of these surgeries, would they be held liable to cover additional surgeries when the animal organs start to fail? Is the financial, emotional, ethical and moral cost of performing a xenotransplantation worth the potential of lengthening one's life? Is it worth it, from the patient's perspective, to consent to this type of surgery knowing the quality of their life post op? Unlike

other perspectives of xenotransplantation that have some technical research completed already but may lack the moral or ethical components, this lacks all three components and therefore requires more research.

The State of Immune System Rejection in Regards to Xenotransplantation

While it's true that given the current track record of xenotransplantation there isn't yet enough development into immunosuppressive drugs there is hope for the future. Researchers at Harvard have discovered through the use of the CRISPRCas9 gene editing system that it's possible to insert portions of the human genome into pigs thus tricking the human immune system into not recognizing the animal organ. While this research is still in its infancy this holds promise that immunosupressive drug therapy may not be the only answer to hyperacute rejection; perhaps in conjunction with more heavily genetically engineered animal organs we could find a solution.

On the Topic of Informed Consent

I do not wish to try and counter this argument nor does anyone working in the field. The issues brought up regarding informed consent specifically with xenotransplantation have not been addressed yet. Perhaps this is because there has only been a very limited amount of 'successful xenotransplantations' and the only one that would've considered the ethical aspect of informed conset was the case that took place in January of last year. However, that case did not have difficulty in regards to informed consent because the organ recepient was ineligible for a human organ transplant and was fully aware of the risks involved even calling the surgery a 'shot in the dark'. We've yet to move far enough into research to a point where clinical trials are occuring regularly, and in theory that would have to happen before xenotransplantation took

place in hospitals regularly. Those interested in building a framework for the field through discourse and consensus could discuss how to handle informed consent. It's important to note that physicians should (in theory) handle it just as they would if it were another invasive surgery except in tailoring the informed consent to the patient's specific needs. Additionally, It would be important to have religious staff available in order to discuss the necessary aspects of xenotransplantation with the patient.

Should Xenotransplantation Research Proceed?

Given the relevant history of the field as well as the current meta of the field of xenotransplantation were to become commonplace much more research needs to be done. But I do believe the research is worth doing, as long as we proceed with extreme caution. To ensure the future of xenotransplantation we have to focus on the safety of it for human application, ethicists and policy-makers generally agree that researchers should first perform preclinical studies in animals [animal-animal transplants] (Olakanmi & Purdy 2). Only *after* these animal experiments suggest the practice and techniques are safe and effective can we say that there is a good and legitimate basis upon which to proceed with human clinical trials. Discovering when to jump from animal trials to clinical trials is the task of society as a whole, through concensus (Olakanmi & Purdy 2). The benefit to humanity and the lives that could be saved through the alleviation of the organ donation waitlist outweigh the associated costs. Additionally if we have the opportunity to save or extend human life we should carefully examine the opportunity in further detail. In regards to xenotransplantation, if it were to become a useful technique in the future, it may still not always be viable depending on the physical condition and pre existing health condition(s) of the patient.

Xenotransplantation, if in the future is viable, would not only alleviate some of the stress off of the organ donation waitlist but could help save or extend some of the lives of people on that waitlist. In many cases, people pass away while awaiting the possibility of an organ transplantation. It's even possible that if developed further, there may come a time where the supply of readily available organs finally outweighs the demand.

"The sale of human organs on the black market has been a huge issue, where people from third-world countries often sell their organs to agents who then barter with people with enough money to buy such organs for their own use" (Regoli 1). This rarely discussed element of organ transplantation has become worse in recent years as it involves the element of exploitation. Additionally, there have even been links to organized crime. Another problem with this situation is that even if one has the funds for purchasing an organ from a willing donor there are still risks involved due to the lack of regulatory oversight. Xenotransplantation has the possibility to affect black market organ sales in a positive manner by providing an alternative solution to using just human organs. Distributive justice inevitably will become a concern however, one that healthcare representatives and ethicists will have to tackle through discourse and consensus.

It's at this point where it becomes important to recognize the general consensus in society which in terms of xenotransplantation research is 'proceed with caution'. In order to move forward within this research field there are many aspects of the moral and ethical framework that need to be discussed my medical professionals and ethicists alike, such as: the moral dilemmas regarding animal usage, the potential for disease transmission from animals to humans, the shorter lifespan of animal organs, the risk of immune system rejection of the transplanted organs and the issue of informed consent. Truthfully, a monetary value cannot be placed on the sanctity of human life and this should be the factor driving research forward.

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