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EDITORIAL

Xenotransplantation - Past, Present, and Future

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The US Food and Drug Administration provides a definition of xenotransplantation as any procedure that involves transplantation, implantation, or infusion of either live cells, tissues, or organs from a nonhuman animal source into a human recipient [1]. The advance in xenotransplantation has left a trail of admiration, excitement, anticipation, confusion, conflicts, and even some fear and anxiety within the medical world and people at large.

The concept of xenotransplantation and the desire of man to merge some physical features of animal species with humans has been linked to the depiction of the mythological Lamassu, a creature bearing a human head and a bull's body, sometimes with horns and ears of a bull during Neo-Assyrian period (720-705 BC). But reports of actual attempts at xenotransplantation began to appear a lot later. If one considers blood as an organ, then the first organ xenotransplantation can be considered to have occurred in the 17th century, when Jean Baptiste transfused blood from animals to humans [2]. The transplant must have failed miserably for the procedure to be banned in France. Despite this setback, numerous attempts at transplanting other organs continued. Skin grafts were first done in the 19th century, between humans and various animal species, including sheep, rabbits, dogs, cats, rats, chickens, pigeons, and particularly those from frogs [3,4]. Corneal xenotransplantation from a pig to a human was first attempted in 1838 [5]. In the 1960s, there were attempts at kidney transplants from chimpanzees to humans. Of the 13 recipients of the chimpanzee kidneys, only one lived for 9 months, the rest died within 4 to 8 weeks from either organ rejection or other complications [6]. The recipient who survived for 9 months collapsed and died of acute electrolyte disturbance. Similar results were obtained with kidney transplants from baboons and chimpanzees. The first human heart xenotransplantation was performed in 1964 when a chimpanzee's heart was transplanted into a human who was semi-comatose with severe atheromatous vascular disease and bilateral leg amputations. The heart failed within a few hours as it was not large and strong enough to support the circulation. There was another attempt in 1983 when a baboon's heart was transplanted into an infant. The infant too died 20 days later due to acute rejection [7]. Numerous liver transplants from baboons to humans were done in the 1960s and 1990s but without significant success [8]. A pig-to-human liver xenograft was also attempted in the 1990s but without much success [9].

Based on the report from the Director of the Xenotransplantation program on June 6, 2022, the cause of death of the first human recipient of a pig's heart was diastolic heart failure [10]. The exact cause and the mechanism for the diastolic heart failure in this patient remain unknown. The heart had evidence of accumulation of interstitial fluid, with extravasation of red blood cells and some fibrosis. Porcine cytomegalovirus (PCMV) DNA was detected in the recipient's circulation and the virus itself was later found present in the transplanted heart and in the spleen of the pig that missed the preoperative screening. It is unclear if the presence of the PCMV had caused harm to the xenograft.

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Incidentally, the presence of PCMV in a pig kidney transplant had been found to shorten the survival of the kidney in baboons [11]. There was no sign of acute rejection, which was believed to have been prevented by three of the ten gene edits that were done on the pig. According to the Director of the program, although the transplant procedure went well, the frail state of the recipient going into the procedure, coupled with the numerous surgical interventions that had to be undertaken over the next few days following the transplant, including one for a type-A aortic dissection, may have contributed to his death some sixty days after the transplant was performed. Despite the death of the recipient, the surgeons remained optimistic and considered it a huge learning experience. Now, whether this transplant in a more suitable patient would have had a better outcome, remains debatable. But what seems certain is that there is still so much that remains to be learned about xenotransplantation, particularly from animals to humans. We are still some way from successful xenotransplantation.

Several reasons have been given for the choice of the pig as a potential organ donor. Firstly, pig organs are anatomically similar to those of humans. Secondly, pigs have large litters and are easy to breed. Thirdly, pigs are considered more suitable for genetic engineering. The advent of more sophisticated genetic engineering tools has reduced the time required to produce a pig with a homozygous knockout of a specific gene from more than 2 years to 5 months [12]. Fourthly, the risk of viral transmission is lower than that from large primates. Besides, large primates are considered endangered species. Many also think that since millions of pigs are bred and killed for human consumption there may, therefore, not be that many ethical issues to address. Some societies or communities may, however, beg to differ on this.

So, What Next for Xenotransplantation?

As we know, unlike allotransplantation, xenotransplantation poses its own unique immunological, physiological, and pathobiological barriers. These have, in many ways, contributed to the slow progress in xenotransplantation. The 80 million years of evolutionary diversion, particularly between pig and man, may not be that easy to bridge. Finding a matching animal species is itself difficult. They have to be matched, for size and anatomy, physiological function, and even perhaps lifespan. Although the transplantation of pig kidneys and hearts into nonhuman primates has shown some encouraging results, the challenge to reproducing these in humans remains enormous. In general, laboratory to clinical application has not always been straightforward or instantly successful. The same can be expected of xenotransplantation. It might still be many more years away before we see it being realized. The development of improved methods of genome editing and the introduction of new immunosuppressive drugs has, no doubt, helped make significant progress in overcoming some of the immunological barriers associated with xenotransplantation. Much, however, still remains to be achieved, particularly in terms of physiology. Would a heart from a four-legged animal where the impact of gravity is a little different, for example, perform as efficiently when transplanted into an upright two-legged human? What will be the impact of gravity and circulatory resistance on the size and function of the transplanted heart even after editing some of the hypertrophy genes? Would it have the capability of adapting to the new physiological demands of the human recipient? It has been reported that transplanting two kidneys from a chimpanzee into a human was inadequate to cope with the renal workload of the human recipient. The pig's body temperature is some 2-3 degrees Celsius higher than that of humans. How would the xenograft cope with the relative hypothermic environment? Would organs from a pig that has a lifespan of 15-20 years last long enough when transplanted into e.g. a 40-year-old human? Would they need new transplants every 12-15 years? What of the microbiological barriers? We know that the cytomegalovirus is species-specific, but can we ensure that it is completely removed from the organ before transplant? What is the risk of zoonotic diseases, should a microbe miss the pre-operative screening? Thus, while providing a designated laboratory-grown pathogen-free and bio-compatible pigs in isolation is ideal, the associated cost may limit its availability only to the wealthy. However, cost-effectiveness analysis may potentially demonstrate that shorter hospital stays

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and fewer immunosuppressive therapies could provide a reasonably better option. What will be the impact of xenotransplantation on allotransplantation? Will it be positive or negative?

In addition to the pathobiological and physiological barriers to xenotransplantation, there are also societal and religious concerns related to xenotransplantation. Not much has been said or discussed on the views of believers of the major faiths like Hinduism, Buddhism, Judaism, Christianity, Islam, and Sikhism. Islam and Judaism clearly forbid the consumption of pork products, but the role of its organ as a life-saving means had received more permissive views, while commanding more discussions and evaluations [13, 14, 15]. Similarly, the predominant faiths originating from the Indian subcontinent, including Hinduism, Buddhism, and Sikhism also have concerns about xenotransplantation. These will have to be addressed along as progress is made in xenotransplantation.

What happens when we have a xenograft and an allograft and two equally compatible recipients - who gets the xenograft and who gets the allograft? How would we decide? Do we need a restriction on the kind of xenografts that can be permitted? An extensive systemic review has recently provided some insight on xenotransplantation and the inherent ethical concerns that it raises [16]. Thus, there is an urgent need to develop some criteria to determine the recipients before xenotransplantation becomes widely available.

The recent advances and growing demands for bioartificial organ substitutes, which are able to be implanted or integrated into a human body and interfacing with living tissues are potential breakthroughs in the medical world. The 3D printing of the liver, heart, and tubular organs, to skin, cornea, and placenta are some of the challenging and exciting areas in tissue engineering and regenerative medicines [17]. Perhaps this will be a better alternative than xenotransplantation with lesser ethical issues.

Clearly, despite the significant progress that has been made in the procedures for xenotransplantation, and understanding of the numerous barriers to it, much still remains to be done before it can progress to a meaningful clinical application. Nevertheless, xenotransplantation experiments continue to provide new information and will no doubt eventually help resolve the issues related to the shortage of human organs for transplant.

REFERENCES

1. US Food and Drug Administration (FDA) Website: https://www.fda.gov/vaccines-blood-biologics/xenotransplantation. Accessed 28 June 2022.
2. Roux FA, Sai P, Deschamps JY. Xenotransfusions, past and present. Xenotransplantation. 2007; 14:208–216. [PubMed: 17489860].
3. Gibson T. Zoografting: A curious chapter in the history of plastic surgery. Br J Plast Surg. 1955; 8:234–242. [PubMed: 13269743].
4. Cooper DKC. Xenografting: The early, early years. Xeno. 1997; 5:21–22.
5. Hara H, Cooper DK. The immunology of corneal xenotransplantation: A review of the literature. Xenotransplantation. 2010; 17:338–349. [PubMed: 20955291].
6. Reemtsma K, McCracken BH, Schlegel JU, Pearl MA, Pearce CW, Dewitt CW, et al. Renal heterotransplantation in man. Ann Surg. 1964; 160:384–410. [PubMed: 14206847].
7. Bailey LL, Nehlsen-Cannarella SL, Concepcion W, Jolley WB. Baboon-to-human cardiac xenotransplantation in a neonate. JAMA. 1985; 254:3321–3329. [PubMed: 2933538].
8. Starzl TE, Fung J, Tzaki A, et al. Baboon-to-human liver transplantation. Lancet. 1993; 341:65–71. [PubMed: 8093402].
9. Makowka L, Wu GD, Hoffman A, et al. Immunohistopathologic lesions associated with the rejection of a pig-to-human liver xenograft. Transplant Proc. 1994; 26:1074–1075. [PubMed: 8029835].
10. Steve Stiles. Cause of death in pig heart recipient: New Clues – Medscape - Jun 13, 2022. https://www.medscape.com/viewarticle/975494?src=WNL_trdalrt_pos1_ous_220616&uac=

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https://doi.org/10.24191/jchs.v7i2.19280

396298FZ&impID=4337434#vp_3. Accessed 4 August 2022.

11. Yamada K, Tasaki M, Sekijima M, Wilkinson RA, Villani V, Moran SG, Cormack TA, Hanekamp IM, Hawley RJ, Arn JS, Fishman JA, Shimizu A, Sachs DH. Porcine cytomegalovirus infection is associated with early rejection of kidney grafts in a pig to baboon xenotransplantation model. Transplantation. 2014 Aug 27;98(4):411-8. doi: 10.1097/TP.0000000000000232. Erratum in: Transplantation. 2014 Oct 15;98(7):e77. Hawley, Robert J [added]. PMID: 25243511; PMCID: PMC4176773.
12. Butler JR, Ladowski JM, Martens GR, Tector M, Tector AJ. Recent advances in genome editing and creation of genetically modified pigs. Int J Surg. 2015 Nov;23(Pt B):217-222. doi: 10.1016/j.ijsu.2015.07.684. Epub 2015 Jul 29. PMID: 26231992.
13. Hunter J. Three ethical issues around pig heart transplants. BBC News. January 11, 2022. https://www.bbc.com/news/ world-59951264. Accessed 28 June 2022.
14. Hammad Sarfraz. An Islamic Perspective on Pig-To-Human Heart Transplant. T-Magazine. https://tribune.com.pk/story/2341120/an-islamic-perspective-on-pig-to-human-heart-transplant. Accessed 4 August 2022.
15. Padela, AI, Duivenbode, R. The ethics of organ donation, donation after circulatory determination of death, and xenotransplantation from an Islamic perspective. Xenotransplantation. 2018; 25:e12421. https://doi.org/10.1111/xen.12421.
16. Kwisda K, White L, Hu€bner D. Ethical arguments concerning human- animal chimera research: a systematic review. BMC Med Ethics. 2020; 21:24.
17. De Bartolo L, Mantovani D: Bioartificial Organs: Ongoing Research and Future Trends. Cells Tissues Organs 2022; 211:365-367. doi: 10.1159/000518251.