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IV.3.4 Xenotransplantation

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Xenotransplantation concerns the transplantation of an organ or tissue of a given type of animal to another type of animal or to a human being. This type of transplantation has gained interest because of the shortage of human organ donations. At the end of the 20th century there was great enthusiasm about xenotransplantation, especially because of a few noted successes: a Chimpanzee kidney was only rejected after nine months, and a Baboon heart was rejected in a human baby after a few weeks. In general, those successes were limited and the enthusiasm had dwindled at the beginning of the 21st century [1: G. Blancho. Editorial xenotransplantation. Curr Opin Organ Transplant. 2009/03/21 ed 2009, 14, 147 doi:10.1097/MOT.0b013e3283292595.]. In particular, the exposure of immunogenic antigens on the animal donor tissue was found to elicit more rejection reactions than hoped for. These rejection reactions were also found to be less easily treated than when the organs came from human donors. Getting this problem under control was, however, a prerequisite for obtaining a usable graft survival. The chosen solution direction involved the genetic modification of donors, mostly pigs [2: D.K.C. Cooper, R. Gaston, D. Eckhoff, J. Ladowski, T. Yamamoto, L. Wang, H. Iwase, H. Hara, M. Tector and A.J. Tector. Xenotransplantation-the current status and prospects. Br Med Bull. 2017/12/12 ed 2018, 125, 5-14 doi:10.1093/bmb/ldx043.] Genetic modification has been easier since 2014 with the introduction of the CRISPR-cas9 technique. The first human xenotransplantation successes were expected with transplantation of genetically modified cells derived from pig islets of Langerhans. [3: D.K.C. Cooper, R. Gaston, D. Eckhoff, J. Ladowski, T. Yamamoto, L. Wang, H. Iwase, H. Hara, M. Tector and A.J. Tector. Xenotransplantation-the current status and prospects. Br Med Bull. 2017/12/12 ed 2018, 125, 5-14 doi:10.1093/bmb/ldx043.] In 2022, however, a man in Maryland (USA) received a heart from a cloned pig in which 10 genes had been modified. [4: B.P. Griffith, C.E. Goerlich, A.K. Singh, M. Rothblatt, C.L. Lau, A. Shah, M. Lorber, A. Grazioli, K.K. Saharia, S.N. Hong, S.M. Joseph, D. Ayares and M.M. Mohiuddin. Genetically Modified Porcine-to-Human Cardiac Xenotransplantation. N Engl J Med. 2022/06/23 ed 2022, 387, 35-44 doi:10.1056/NEJMoa2201422.] The initial course was prosperous. After 49 days, severe thickening of the heart muscle developed; 60 days after transplantation, the patient died. At autopsy, necrosis (death) of cardiac myocytes was seen. The cause was multifactorial: rejection, an immune response to the administered human immunoglobulins and activation of porcine CMV virus. [5: M.M. Mohiuddin, A.K. Singh, L. Scobie, C.E. Goerlich, A. Grazioli, K. Saharia, C. Crossan, A. Burke, C. Drachenberg, C. Oguz, T. Zhang, B. Lewis, A. Hershfeld, F. Sentz, I. Tatarov, S. Mudd, G. Braileanu, K. Rice, J.F. Paolini, K. Bondensgaard, T. Vaught, K. Kuravi, L. Sorrells, A. Dandro, D. Ayares, C. Lau and B.P. Griffith. Graft dysfunction in compassionate use of genetically engineered pig-to-human cardiac xenotransplantation: a case report. Lancet. 20230629 ed 2023, 402, 397-410 doi:10.1016/S0140-6736(23)00775-4.] In 2023, a kidney from the same genetically modified pig species remained functioning properly for a week in a brain-dead patient with renal insufficiency. After a week, support (including ventilation) of the brain-dead patient was discontinued. The kidney transplant was functioning very well at that time and no signs of rejection were visible under the microscope either. [6: J.E. Locke, V. Kumar, D. Anderson and P.M. Porrett. Normal Graft Function After Pig-to-Human Kidney Xenotransplant. JAMA Surg. 20230816 ed 2023 doi:10.1001/jamasurg.2023.2774.] This result possibly means that xenotransplantation with organs from genetically modified animals has moved closer to application in humans.

In addition, in xenotransplantation, the transmission of animal viruses to human beings proves to be a clear risk [7: L. Scobie and Y. Takeuchi. Porcine endogenous retrovirus and other viruses in xenotransplantation. Curr Opin Organ Transplant. 2009/05/27 ed 2009, 14, 175-179 doi:10.1097/mot.0b013e328327984d.]. Also with regard to

this problem, genetic modification using the CRISPR-cas9 technique is hoped to move forward: viruses present in DNA could be “cut” out of the DNA using this technique. The genetically modified pigs used in 2022 and 2023 would not carry the porcine endogenous retrovirus. Nevertheless, the porcine-CMV virus appeared to be transmitted and less treatable than the human equivalent. [8: B.P. Griffith, C.E. Goerlich, A.K. Singh, M. Rothblatt, C.L. Lau, A. Shah, M. Lorber, A. Grazioli, K.K. Saharia, S.N. Hong, S.M. Joseph, D. Ayares and M.M. Mohiuddin. Genetically Modified Porcine-to-Human Cardiac Xenotransplantation. N Engl J Med. 2022/06/23 ed 2022, 387, 35-44 doi:10.1056/NEJMoa2201422.]

In 2001, the Pontifical Academy for Life dedicated a symposium to this subject, in order to respond to a number of questions of a moral nature with respect to xenotransplantation. The symposium highlighted, first of all, three anthropological and ethical issues relevant to the question of whether xenotransplantation, as such, is a good act [9: Pontifical Academy for Life. Prospects for xenotransplantation scientific aspects and ethical considerations. Vatican City 2001.]:

1. The acceptability of human intervention in the created order.
2. The ethical acceptability of using animals to increase the Medical Care for Life: Therapeutic Interventionchance of survival of human beings and to increase their wellbeing.
3. The possible objective and subjective influence which an organ or tissue of animal origin can have on the identity of the human recipient.

3.4.1 The acceptability of intervention in the order of creation

According to the created order, man, created in God’s image and likeness, has a central place. The lower creatures serve man, and he has a limited right of disposal over them. The purpose of this central position of man is not so much his lordship over other creatures, but his cooperation with the Creator in fulfilling the purpose of creation: “Be fruitful and multiply, and fill the earth and subdue it” (Gen 1:28). The “creatures which are lower in the order of creation” must serve and be subservient to this particular task. In this light, xenotransplantation is acceptable.

3.4.1.1 The use of animals for man

In virtue of their being created beings, animals have their own worth, which man must value and respect. God placed the animals, together with other non-human creatures, at the service of man. Still, they, too, are God’s creatures, and it is, therefore, important, in the use of animals, to be alert as to whether there is a necessity for doing so and whether the chosen use does not cause the animal unnecessary suffering.

3.4.1.2 The influence on the identity of the recipient

As explained earlier, it is morally wrong to implant a foreign organ which changes the identity of the person [10: S. Ioannes Paulus II. Ad eos qui conventui de chirurgicis transplantationibus interfuerunt (29-8-2000). Acta Apostolicae Sedis 2000, 92, 822-828.] [11: Pius XII. Vous nous avez demandé. Toespraak tot de Italiaanse Vereniging van hoornvliesdonors en de Italiaanse bond van blinden en tot oogspecialisten, over de morele waardering van de hoornvliestransplantatie (14 mei 1956). Acta Apostolicae Sedis, Rome: Libreria Editrice Vaticana; 1956, 48.] [12: Pontifical Academy for Life. Prospects for xenotransplantation scientific aspects and ethical considerations. Vatican City 2001.]. This issue does not arise in the transplantation of a heart, kidney or liver. Brains and genital organs, however, are inseparably united to the identity of the human person (cf. the present Chapter 3.5). Given the effect of the transplantation of the organs mentioned on the identity of the person, they are not permitted.

In conclusion, as long as the identity of the human recipient is not affected, xenotransplantation is acceptable, as long as the risks are proportionate, which, as will become evident later, turns out to be a great difficulty [13: Pontifical Academy for Life. Prospects for xenotransplantation scientific aspects and ethical considerations. Vatican City 2001.].

There are, however, a number of aspects which require more attention:

1. The risks to the recipient.
2. The use of organs and tissues derived from transgenic animals.
3. The allocation of the healthcare means.
4. The patentability in xenotransplantation

3.4.2 The health risk to the recipient

A number of risks are already evident. First, there is the chance of rejection. At present, this chance is high and the suppression of the immune system will therefore have to be more radical. It is certain that the recipient has a high chance of physical and mental damage from the rejection as such, as well as from the immunosuppressive therapy. One also fears that xenotransplantation can cause animal viruses to be transmitted to human recipients. The risks of transmission of the Porcine Endogenous Retrovirus (PERV) and Hepatitis E (HEv) are not fully clear [14: L. Scobie and Y. Takeuchi. Porcine endogenous retrovirus and other viruses in xenotransplantation. Curr Opin Organ Transplant. 2009/05/27 ed 2009, 14, 175-179 doi:10.1097/mot.0b013e328327984d.]. No transmission of these viruses was observed in initial studies of humans who had had contact with pig tissues or studies in which pig tissues were transplanted to non-human primates (monkeys) [15: D.K.C. Cooper, R. Gaston, D. Eckhoff, J. Ladowski, T. Yamamoto, L. Wang, H. Iwase, H. Hara, M. Tector and A.J. Tector. Xenotransplantation-the current status and prospects. Br Med Bull. 2017/12/12 ed 2018, 125, 5-14 doi:10.1093/bmb/ldx043.]. However, to completely avoid the problem of virus transmission, good practices regarding selection of not severely infected animals and possibly genetic modification of these animals still need to be developed.

3.4.3 Transgenesis

In order to optimise the chance of survival of organs in human beings, the genetic modification of the potential animal-donors seems to be an obvious option. The donor pigs used in 2022 and 2023 were genetically modified with 3 knockouts and 7 gene modifications, which would reduce the organs' rejection reactions after transplantation. The changing of the genetic make-up of animals is acceptable as long as a number of ethical principles are taken into consideration:

1. The changes resulting from the genetic modifications may not cause the animal pain, fear, and suffering.
2. The effects on the offspring of the human recipient and the environment must be taken into consideration.
3. Transgenic animals must be well-controlled and may not just be set free in the environment.
4. The number of transgenic animals which is brought into being for the purpose of transplantation must be kept to a minimum.
5. The removal of organs and/or tissue must be carried out in one single surgery.

6. Every experiment must be judged by a competent ethical commission.
   It is also important that recipients are fully informed about the origin of the organs and the accompanying risks and that one obtain from the recipients an informed consent for the procedure (Pontifical Academy for Life 2001, no. 15-16) [16: Pontifical Academy for Life. Prospects for xenotransplantation scientific aspects and ethical considerations. Vatican City 2001.].

Not all Catholic ethicists, though, agree with this point of view of the Pontifical Academy for Life. [17: N. Tonti-Filippini, J.I. Fleming, G.K. Pike and R. Campbell. Ethics and Human-Animal Transgenesis. National Catholic Bioethics Quarterly 2006, 6, 689–704.] Tonti-Filippini, Fleming, Pike and Campbell are opposed to the intentional mixing of human DNA with that of animals.

1. In the first place they read a prohibition not only of hybridisation in the sense of fertilisation between human and animal gametes, but of any human-animal transgenesis in Donum Vitae (I,6). [18: Congregatio pro Doctrina Fidei. Donum Vitae. Instructio de observantia erga vitam humanam nascentem deque procreationis dignitate tuenda. Acta Apostolicae Sedis 1988, 80, 70-102.] They are of the opinion that the term ‘hybrid’ does not only mean an organism having its origin in a fertilisation process, but any organism of which its inherited characteristics stem from organisms of different species. Therefore, the Congregation for the Doctrine of the Faith would condemn in its instruction Donum Vitae apart from hybridisation by means of fertilisation of human and animal gametes every form of human-animal transgenesis.
2. Secondly, they are convinced that human-animal transgenesis of whatever proportion, also in the case of the transmission of one human gene to an animal ovum or zygote, causes an unacceptable confusion of identity.

A hybrid resulting from fertilisation of a human and an animal gamete has a full set of genes from human origin. Even if it would become a full-grown individual without specific human features as rational capacities and the capacity of free decision making, one could not by all means exclude that it is animated by a human soul and hence a human person. For the presence of the full set of genes from the animal part could prevent the spiritual faculties from coming to expression. It is of course impossible to say which proportion of human-animal transgenesis would result in an organism with the ‘disposition of the material’ (see this Manual II.1.1.2.4) to be animated by a human soul. The Pontifical Academy obviously supposes that this is not the case when only one or a few human genes, especially those which might prevent a immunological rejection of an organ from the resulting organism after transplantation to humans, are added to the genome of an animal ovum or zygote, and that this is therefore morally licit. However, it is a fact that not all Catholic ethicists share this view. Tonti-Filippini, Fleming, et al. think that “the confusion of identity arises as soon as any human genes become formative of the new being” [19: N. Tonti-Filippini, J.I. Fleming, G.K. Pike and R. Campbell. Ethics and Human-Animal Transgenesis. National Catholic Bioethics Quarterly 2006, 6, 689–704.] and that the transmission of only one human gene to an animal ovum or zygote is an infringement on human dignity and an abuse of the human generative faculties (they do however not reject adding human genes to bacteria, because these cannot develop into embryos, such that no confusion of identity will arise).

3.4.4 Allocation of healthcare resources

The development and implementation of xenotransplantation demands the investment of some of the resources available for healthcare. These resources, when invested in xenotransplantation, cannot be used for other purposes in healthcare. A thorough analysis of costs and benefits is therefore inevitable [20: Pontifical Academy for Life. Prospects for xenotransplantation scientific aspects and ethical considerations. Vatican City 2001.].

3.4.5 Patentability

Without doubt, private companies have invested much money and energy in the development of xenotransplantation. The application for a patent is therefore a logical step for such companies. Patents, however, lead to higher costs for the consumers, in comparison to non-patented products. Even though there is no moral objection to patents, as such, it is important to guarantee that the recipients will have equal access to healthcare, without any form of discrimination and impediments based on higher costs [21: Pontifical Academy for Life. Prospects for xenotransplantation scientific aspects and ethical considerations. Vatican City 2001.].