

The ethics debate in relation to xenotransplantation

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Summary

Xenotransplantation is the transplantation of organs and cells from one species to another: it has enormous potential to increase the supply of organs and tissues to alleviate human disease. Recent scientific progress has eliminated the obstacle of hyperacute rejection, which is the massive destruction of the transplanted organ within 24 h. Despite this progress and the tremendous clinical potential, a number of ethical issues require careful consideration. These issues involve the human recipients, source animals, biotechnology companies and ultimately, the general public. One of the greatest concerns is the potential risk that an infectious agent will be transferred with the organ to the recipient, from whom it may spread, leading to a possible epidemic. However, there is no current evidence that porcine endogenous retrovirus, which is the agent of greatest concern, will be pathogenic. Using modern biotechnology, it may be possible to generate pigs that are free of this virus in the near future. Addressing these issues deliberately and in a scientific manner, with public involvement and education, will result in a greater understanding of the risks and benefits of xenotransplantation. This knowledge can then be utilised to fulfil the increasing demand for transplantable organs, with minimal risk.

Keywords

Endothelium – Ethics – Genetic engineering – Organ transplantation – Pig – Porcine endogenous retrovirus – Thrombotic microangiopathy – Xenotransplantation – Xenozoonosis.

Introduction

The success of clinical organ transplantation has resulted in a steady increase in the demand for organs and tissues. Unfortunately, methods to increase the number of organs, such as using 'marginal' (less than optimal) organs from deceased human donors, increasing public awareness of the need for donation, and using living donors (e.g. living donor kidney or partial liver donation) have not met this increasing demand. There are currently more than 87,000 patients on the waiting list for organ transplantation in the United States of America (USA) alone, and yet only approximately 25,000 solid organ transplants will be performed in 2005 (23), of which only 18,000 will involve organs from deceased subjects.

Xenotransplantation involves the transplantation of organs, tissues, or cells from one species to another (6, 8, 10). Of major interest, of course, is transplantation from animals into humans, which has enormous potential to fulfil the demand for transplantable organs, tissues and cells to alleviate disease and save human lives. Initially, the ideal source animals were thought to be nonhuman primates, since these are close to humans phylogenetically and therefore represent the best immunological match. However, for a number of reasons (Table 1), current opinion now favours the use of the pig as the source animal (9). Biotechnology is developing rapidly, which it is hoped will enable us to overcome the many immune-related and other difficulties that xenotransplantation presents. The prospect that this form of surgical therapy will become a clinical reality is drawing closer (8).

Table I
Factors determining the suitability of pigs as potential donors of organs and tissues for humans

| Factors | Pigs |
|--|--|
| Availability | Unlimited |
| Breeding potential | Good |
| Period to reproductive maturity | 4-8 months |
| Length of pregnancy | 114 + 2 days |
| Number of offspring | 5-12 |
| Growth | Rapid (adult human size within 6 months) * |
| Size of adult organs | Adequate |
| Cost of maintenance | Low |
| Anatomical similarity to humans | Moderately close |
| Physiological similarity to humans | Moderately close |
| Relationship of immune systems to humans | Distant |
| Knowledge of tissue typing | Considerable (in selected herds) |
| Necessity for blood type compatibility with humans | Probably unimportant |
| Experience with genetic engineering | Considerable |
| Risk of transfer of infection (xenozoonosis) | Low |
| Availability of specific pathogen-free animals | Yes |
| Public opinion | Favourable |

* Breeds of miniature swine are approximately 50% of the weight of domestic pigs at birth and sexual maturity, and reach a maximum weight of approximately 30% of standard breeds

Current state of the science

Scientific progress in experimental xenotransplantation is steadily advancing. The problem of hyperacute rejection (massive destruction of the transplanted organ within 24 h) has been overcome by the introduction of pigs in which the gene for the enzyme α 1,3-galactosyltransferase has been deleted, so that the endothelium of the blood vessels of the pig no longer expresses the important Gal α 1,3Gal antigen against which humans have natural preformed antibodies (17, 24). An immunosuppressive regimen has been developed that does not result in high levels of infection or malignancy, and yet which controls the rejection response of the graft for periods of two to six months (18).

However, a thrombotic microangiopathy (thrombosis in the small blood vessels) develops in the grafted organ in all cases, probably as a result of low-grade endothelial cell activation by anti-nonGal antibodies or cellular constituents of the recipient's blood. This activation leads to a procoagulant change in the normally anticoagulant status of the endothelium (18). It is hoped that this problem will be overcome by further genetic manipulation of the pig, for example, by introducing a human gene, such

as the tissue factor pathway inhibitor, that will maintain the anticoagulant state of the endothelium.

The physiological activities of the grafted organ have not been investigated in the absence of an immune response, but initial observations would suggest that the porcine heart can function adequately in the primate body environment (18, 31), and that most of the functions of the porcine kidney are also satisfactory after transplantation (28).

The immune barriers and physiological differences between pig and human have been built up over 80 million years of evolutionary divergence between the species. Claus Hammer, who has written extensively on xenotransplantation, has pointed out that, in trying to overcome the barriers to xenotransplantation, we are actually endeavouring to 'outwit evolution': not an easy task (13). Hammer has also suggested that although technologically we are in the 21st Century, ethically we remain in the Middle Ages (13). Although this may be an exaggeration employed for dramatic literary effect, few perhaps would disagree that our technology may be forging ahead faster than consideration of the ethical concerns it raises.

Ethical considerations

Xenotransplantation, as with any other clinical therapy or potential therapy, presents a number of ethical dilemmas that require consideration (3, 6, 13, 19, 25, 32, 33). An evaluation of these dilemmas requires the identification of all who are directly involved in, and of those who may potentially be affected by, xenotransplantation. This includes potential human recipients, physicians, scientists, biotechnology personnel, and the general public, as well as the source animals.

The ethical appropriateness of any clinical trial depends on many interacting factors, not least the state of the science. Indeed, if the science is sufficiently advanced, and the potential benefit to patients is almost assured, then it may be unethical and irresponsible not to initiate a clinical trial. In contrast, if the science is not sufficiently advanced, then the trial is inappropriate. If the science may just be sufficiently advanced, other factors come into play. An attempt will be made below to discuss some of the factors that must be weighed in making the decision to progress to clinical trials in regard to xenotransplantation.

Ethics and potential risks of allotransplantation

It should not be forgotten, however, that xenotransplantation would render obsolete the numerous ethical questions relating to human allotransplantation

(transfer of organs, tissues or cells between individuals of the same species). These include the illegal trade in the sale of organs from living donors, the use of condemned prisoners as donors in some countries, and the controversial question of whether living donors or the families of deceased donors should receive financial rewards for their donation. These topics have been discussed elsewhere (10).

Although there are unknown risks in clinical allotransplantation, some of which may result from incomplete information about the donor, these risks are usually minimal, although exceptions still occur. For example, the risk of the transfer of infection with the human donor organ cannot be overlooked. One or more infectious agents are almost always knowingly transferred from donor to recipient, e.g. cytomegalovirus, Epstein-Barr virus, and hepatitis B or C, and sometimes even human immunodeficiency virus (HIV). The list of diseases that have been transferred with a donor organ is continually growing, as exemplified by the transfer of rabies and West Nile virus in recent months. If there is a suspicion of a possible risk (e.g. a donor with negative laboratory results, but high-risk behaviour for HIV infection), this information will be passed on to the patient who can then decide whether or not to accept the organ.

Ethical issues relating to potential human recipients of xenotransplants

The potential subject, a patient with end-stage organ failure, is entitled to the same rights, respect, autonomy, and voluntary informed consent that are necessary for all human subjects (2). However, owing to uncertainty in the risk analysis it may be difficult to guarantee that the first patients that agree to undergo xenotransplantation will truly be fully informed (5). There may be risks that are not yet known and which, therefore, are unable to be quantified.

Apart from the inherent risks associated with the introduction of any new form of medical therapy, the one specific risk of xenotransplantation that has gained most attention is that of the transfer of a porcine infectious agent to the human organ recipient, and more importantly, from the recipient to his/her family, friends, and medical attendants (4, 20, 27, 29).

There are, however, several advantages in this respect to be gained from xenotransplantation. First, the organ will be retrieved from a pig whose health status has been thoroughly monitored and is fully known, in marked contrast to the human organ donor. If an infectious agent is inadvertently present in the pig at the time of transplantation, it is possible that it is with a species-

specific microorganism, which will not be of risk to the recipient (21). For example, strains of cytomegalovirus are species-specific (i.e. the strain only infects a specific species, e.g. pigs, and is unable to infect other species, e.g. humans). In experimental models, there has been no transfer of porcine cytomegalovirus from the transplanted pig organ to the nonhuman primate recipient.

Steps are being taken to breed herds of organ-source pigs that are free of all known infectious agents. From a risk assessment perspective, it would seem reasonable and acceptable to transplant organs from pigs in which the presence of all known exogenous organisms of significance has been excluded. To delay a clinical trial because of the potential risk of unknown microorganisms would seem illogical, since there will always be an 'unknown' to any scientific endeavour.

Nevertheless, the possibility of the transmission of a porcine endogenous retrovirus (PERV) may persist (27, 29, 32). Porcine endogenous retroviruses are viruses or virus particles that have existed in the nucleus of all pig cells for thousands, if not millions, of years. Although they appear to do the pig no harm, and their human counterparts do humans no harm, there is concern that infection of human cells by pig viruses may be pathogenic and lead to conditions such as immunodeficiency or malignancy. However, there is no current evidence that they will be pathogenic, and with modern biotechnology it is possible that pigs that are free of PERV may be produced within the next few years (16).

Because of the potential risk for transfer of infection, potential subjects will need to realise that their participation in any clinical trial of xenotransplantation will require them to commit to life-long surveillance, which will be much greater than the requirements for those transplanted with a human organ. As part of the informed consent procedure, it is always clearly stated that a subject in any clinical trial has the right to withdraw from the study. However, once exposed to a pig organ or to pig cells, the human recipient will remain at risk for a porcine infection for the remainder of his or her life, even if the organ is subsequently removed. The patient will therefore need to be followed indefinitely throughout his or her life. It is also likely that the recipient will be expected to consent to the performance of an autopsy at the time of his/her death (3) so that scientists can learn more about the effects of the xenotransplant on the patient's own organs, particularly regarding the presence of any infectious agents that might not have been identified clinically. Due to the potential risk of disease transmission, this surveillance may also need to extend to family members or close contacts of the recipient. Will this invasion of the individual's privacy be considered justified if it is to the potential benefit of the community at large?

Ethical issues relating to the use of animals as sources of organs for humans

There continues to be a great deal of attention directed towards the use of animals in medical research, and people hold widely-differing opinions in this respect. Some individuals are strict vegetarians, do not use any animal products, and strongly oppose all animal research. At the other extreme are those who believe that animals exist for the use of mankind for food, products, research, etc. A discussion of the ethics of animal research in general is beyond the scope of this paper, and the issue here is whether we can ethically justify the use of animals, and specifically pigs, for the purpose of xenotransplantation (12).

Human attitudes towards animals have changed greatly through the centuries, and still vary between cultures. Even within a given society, opinions extend from one extreme (that humans can treat animals as they wish) to the other (that animals have rights equal to those of humans). The middle-of-the road view held by the majority is that animals should be treated humanely and with respect, but are not entitled to all the same rights as humans. Most of us would also accept that the more distant the species is from us phylogenetically (or in evolutionary terms), the fewer rights it has. (A notable exception is provided by endangered species, whose rights may increase substantially.) Animal 'rights' are usually taken to mean that the animal is entitled to be treated as we would treat our fellow human.

The concept has been put forward that a member of one species of animal is not necessarily inferior to a member of another species (15, 26). For example, a healthy chimpanzee, who is an important social member of a group (or extended family) of chimpanzees and who demonstrates a degree of intelligence and emotion with which we can identify, may be a more 'worthy' member of the world's animal kingdom than a severely brain-damaged human subject, who has been in a vegetative state for many years, or an anencephalic infant, who will never be aware that he or she is loved and will never be able to return that love (11).

Our ethical qualms relating to the use of the pig for such purposes are very much reduced in view of the fact that the pig is already purpose-bred as a source of food for humans. It may be that the general public will see this as a more acceptable use of animals than simply as a food source, and readily see its benefit to mankind. Physicians have used heart valves from pigs, animal products, such as insulin, and animal tissue, such as skin grafts for burnt patients, for many years. The use of animals for these forms of treatment has generally been accepted by the public.

The human race has not always had the same concern for animals that it has today. It was only in the 19th Century

that attention began to be paid to the way animals were housed and treated. Legislation regarding animals was part of the social reform movement associated with such other matters as the abolition of slavery, the regulation of child and adult labour, improvement of prison conditions, and reform of education. Today, there continue to be differences of opinion regarding animal rights and certain practices which some people tolerate are not considered acceptable by others. However, there is broad acceptance of the use of pigs to provide food, insulin and heart valves for humans, and in all these cases the pig has to be killed, so those who do not object to the killing of pigs for these purposes should surely have no objection to killing pigs to provide whole organs for transplantation. If we can employ pig heart valves in large numbers, it is surely nonsensical to object to the use of pig hearts. Only extreme vegetarians (who do not eat any form of animal tissue, do not wear leather shoes, etc.) can reasonably raise objections to the use of the pig in xenotransplantation.

Those who breed pigs for organ donation will be regulated by various government bodies to ensure that the animals receive proper care and housing. The high quality of the end product – the donor organs – will be essential if such breeders are to remain in business. Since the livelihood of the breeders will depend on their raising healthy pigs, the animals will be raised under ideal conditions that will certainly exceed those of all farm animals (and even some humans). Indeed, it is unlikely that any animals will ever have been maintained so carefully, with the possible exception of valuable racehorses.

The highest quality of care will be necessary, not only to ensure the organ is in a healthy state, but also to minimise the risk of infection to the pig. They will be housed in specific pathogen-free facilities with excellent nutrition, plenty of social interactions with each other and with animal technicians, and under strict veterinary surveillance. This care will be far superior to that which they would receive if their purpose was to be a source of food. When the time comes for organ retrieval, this will be carried out humanely under full anaesthesia; the animal will die while anaesthetised.

There will therefore be important differences between animals bred for organ donation and those bred (or captured from the wild) for food consumption or medical or pharmaceutical research. The arguments against the use of animals as donors of organs for humans should be significantly fewer than those directed against the use of animals in medical research, and even those against the use of animals for their meat.

The pigs used as a source of organs for xenotransplantation will undoubtedly be genetically-engineered to render their organs resistant to the human immune response. Some believe that the genetic engineering of animals is little

different from selective breeding. Indeed, genetic engineering allows us to achieve the desired goal much more rapidly, but it also allows us to breed genetically-manipulated pigs that would be impossible to obtain by selective breeding. Pigs with human complement-regulatory proteins are one such example. Cloning may prove to be a more efficient way of generating a herd of genetically modified animals. It therefore seems rather simplistic to compare genetic engineering with selective breeding. Concerns have been expressed that there may be late effects of this technology that will place the animals at additional risk.

The genetic engineering will almost certainly include pigs that express one or more human genes. They will contain a small amount of human protein in their cells, which is seen by some as a violation of species boundaries (19). It is suggested that such transgenic pigs could have negative effects on certain ecosystems, for example, if viruses from different species recombine or mutate (19). To eliminate such risks, it is recommended that these pigs be housed in isolation from 'wild-type' pigs.

The United Kingdom (UK) Advisory Group on the Ethics of Xenotransplantation concluded that 'some degree of genetic modification is ethically acceptable' but that 'there are limits to the extent to which an animal should be genetically modified' (22). It did not indicate what those limits might be. This was possibly sensible, as the limits are extremely difficult to define.

In the Netherlands, a committee has been established to oversee all work involving biotechnology and animals (10). The acceptability of any proposed experiment involving animals is based on two guidelines, as follows:

- there must be no unacceptable implications for the health and welfare of the animal
- there must be no serious ethical objections to the procedure. This would presumably rule out alterations to the brain that might modify the thinking capacity of the pig (or of a human recipient of pig cells) or genetic changes that might lead to the reproduction of one species by the other.

Ethical issues relating to the biotechnology industry

If a transgenic pig is developed that plays a key role in the success of xenotransplantation, the question has been asked as to whether it is ethical for the company that breeds these pigs to make a profit from their sale (6). The view has been put forward that surely no profit should be derived from this humanitarian enterprise, just as blood and human organs should not be bought or sold for profit. Only the essential expenses involved in supplying the

blood or organ should be passed on to the recipient or recipient organisation.

The key question is whether the pig organ should be grouped with human donor organs (which are, at least theoretically, provided to the recipients free of charge except for the expenses involved in their procurement), or with other lifesaving 'devices' that have been developed by companies to be sold at a profit? The latter would include pig (and mechanical) heart valves, a multitude of drugs, as well as such equipment as dialysis machines and mechanical cardiac assist devices. All of these save lives, and it is not thought wrong to make a profit from their development and sale. The companies that develop transgenic pigs will expect to make a reasonable profit from their investment of time, money, and resources, and this should surely not be considered in any way unethical or unjustified.

Ethical issues relating to public opinion and safety

An Institute of Medicine committee in the USA pointed out that since the general public derives no direct communal benefit, its fear of, and resistance to, xenotransplantation may increase (15). As in other aspects of xenotransplantation, the role of the media will clearly be important in shaping public opinion in this respect.

As outlined above, the greatest potential risk is that of the transfer of infection with the organ to the recipient, and then, perhaps more importantly, from recipient to members of the public. In the perceived worst-case scenario, xenotransplantation could lead to an epidemic in the human population, similar to the acquired immune deficiency syndrome epidemic (1). The decision to proceed with clinical xenotransplantation must therefore be made with public safety in mind (3), a consideration which is predominant in the minds of those undertaking research in this field (30). The benefits to the potential organ recipient will need to be weighed against the perceived risk, if any, to the general public. Xenotransplantation has been described as having a risk potential that is completely opposite to immunisation programmes (2): immunisation programmes protect a given population while putting a few individuals at risk for adverse reactions, while xenotransplantation will benefit individuals while possibly putting the population at risk of infection (2). If even a small risk to public health exists, public opinion on the wisdom of embarking on a clinical trial of xenotransplantation needs to be taken into consideration.

Reports from groups that to a certain extent reflect the public attitude, namely, the Institute of Biology (14) and the Nuffield Council on Bioethics (22), both in the UK,

have been positive in accepting that xenotransplantation is an ethical way in which to meet the growing demand for transplanted organs.

The benefits and risks of any medical advance have to be carefully weighed using the available facts and expert opinions. A decision to move forward has to be based on evidence that the benefits appear to outweigh the risks. As the potential benefits to individuals or society increase, it becomes warranted to accept slightly increased risks. If the technology leads to great benefits to individuals, we have a moral obligation to accept a small risk to the community, but we also have an obligation to take all possible steps to minimise that risk.

In the USA, federal regulations require that the degree of risk of an experimental procedure to a patient be 'reasonable' in relation to the potential benefit. The benefit

can be either to the patient or to society, which will gain from the knowledge obtained. The Institutional Review Board of the hospital where the procedure is to be performed is expected to assess whether the risk-benefit ratio is justified.

Proceeding in a slow, deliberate fashion, with extensive reviews and discussions, will enable us to fully explore the risks and benefits of xenotransplantation. In this manner, we may be able to use this treatment safely to help the thousands of people who may die waiting for a human organ. Keeping the public informed of each step along the way should increase public support. In the end, however, it is the general public who will have to live with, and possibly pay for, this research endeavour. ■

Le débat éthique lié à la xénotransplantation

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Résumé

La xénotransplantation est la greffe d'organes et de cellules entre espèces. Elle offre d'immenses possibilités d'accroître la quantité d'organes et de tissus disponibles pour faire échec à la maladie chez l'homme. De récents progrès scientifiques ont permis d'éliminer l'obstacle constitué par le rejet hyperaigu, qui correspond à la destruction massive de l'organe transplanté dans les 24 heures qui suivent la greffe. Malgré ce progrès et les formidables possibilités cliniques offertes, un certain nombre de questions éthiques méritent un examen attentif. Ces questions concernent les receveurs humains, les animaux utilisés comme source, les entreprises de biotechnologie et, au bout du compte, le grand public. Une des plus grandes préoccupations reste le risque potentiel qu'un agent infectieux soit transmis au receveur, à partir duquel il peut se propager et conduire possiblement à une épidémie. Cela étant, rien ne prouve actuellement que le rétrovirus endogène porcin, qui est l'agent le plus préoccupant, sera pathogène. Grâce à la biotechnologie moderne, il pourrait être envisagé de produire des porcs indemnes de ce virus dans un avenir proche. La prise en compte de ces questions de façon réfléchie et selon une approche scientifique, conjuguée à une participation et à une éducation de la population, aboutira à une meilleure connaissance des risques et des avantages de la xénotransplantation. Cette connaissance pourra alors être exploitée pour répondre à la demande croissante d'organes transplantables, avec un risque minime.

Mots-clés

Endothélium – Éthique – Génie génétique – Greffe d'organe – Microangiopathie thrombotique – Porc – Rétrovirus endogène porcin – Xénotransplantation – Xénozoonose. ■

El debate sobre la dimensión ética de los xenotrasplantes

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Resumen

Un xenotrasplante es el trasplante de órganos o células de una especie a otra. Esta técnica abre enormes posibilidades para disponer de un mayor suministro de órganos y tejidos destinados a tratar enfermedades humanas. Últimamente, los avances científicos han eliminado el obstáculo que suponía el rechazo hiperagudo, que es la destrucción masiva del nuevo órgano en las 24 horas siguientes al trasplante. Pese a estos adelantos y a su inmenso potencial clínico, hay una serie de cuestiones éticas que merecen detenida reflexión, tocantes a la persona receptora, los animales donantes, las empresas de biotecnología y, por último, el gran público. Uno de los temas que más inquietud suscita es el posible riesgo de transferencia de un agente infeccioso al receptor de un órgano, a partir del cual pueda extenderse y provocar eventualmente una epidemia. Sin embargo, de momento no hay prueba alguna de que el retrovirus endógeno porcino, que es el organismo que más preocupa, vaya a resultar patógeno. Quizá sea posible, en un futuro próximo, obtener cerdos exentos de ese virus utilizando la biotecnología moderna. Si se abordan estas cuestiones de forma consciente y científica, con la participación de la sociedad y con una labor de pedagogía pública, se entenderán mejor los riesgos y beneficios que traen aparejados los xenotrasplantes. Ello puede servir después para responder con un mínimo riesgo a la creciente demanda de órganos trasplantables.

Palabras clave

Cerdo – Endotelio – Ética – Ingeniería genética – Microangiopatía trombótica – Retrovirus endógeno porcino – Trasplante de órgano – Xenotrasplante – Xenozoonosis.



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