



Editorial

Arguments for the ethical permissibility of transgenic xenografting

According to UNOS (United Network for Organ Sharing), 2000 will be another year of severe donor liver shortage for those in the USA awaiting transplant. On 31 October 1999, UNOS reported 66175 registered patients on their national organ transplant waiting list. Of these, 14088 patients are registered for a liver transplant. The 1998 human donor liver pool was only 4487. Previous attempts to address this shortage have included bioartificial livers and extracorporeal liver assist devices,¹ permanent whole organ xenotransplants,² and whole organ xenotransplant bridges.³ The use of non-transgenic animal organs for whole organ transplantation presents technical dilemmas for scientists, namely hyperacute rejection, however, transgenic animals may be able to address this challenge.

It is pertinent to examine society's general views regarding using animals as organ donors. A recently published study⁴ reported a French survey which found over 70% of those polled indicated that they would accept a xenograft organ upon disclosure of the theoretical infectious risk. The British Medical Association News Review⁵ reported results from a survey of 250 British physicians, indicating that 75% of the general practitioners polled were in favor of xenotransplantation. The majority also approved of using transgenics to alter animals for the sake of medical progress. As physician Peter Bamber commented, 'so long as man uses animals for food, I see no moral distinction from the use of non-humans for medical purposes.' Another study⁶ surveyed British renal failure patients, with results indicating that 78% were willing to accept a pig kidney for their transplant. Like Dr Bamber, these patients indicated they saw no moral distinction between pigs bred for human food and pigs bred for saving lives medically. Scientific data aside, xenotransplantation is a controversial topic with various philosophical positions and the uncertain clinical risk of this technology is not the only factor that confers many to view it as ethically impermissible.

Although the purpose of this paper is not to debate the various animal rights positions, a discussion of transgenics and xenotransplantation would not be complete without including the concept of animal rights. Philosopher Jonathan Hughes predicted the future when he argued that animals used for xenotransplantation purposes will almost certainly be removed from their natural environment, forced to live and breed in a contained, unnatural environment, and subjected to genetic manipulation in order to maximize their transplantation potential.⁷ Dr

Hughes' concerns are now reality. In the hygienic breeding farms of companies such as Baxter (Princeton, NJ, USA), Alexion Pharmaceuticals (New Haven, CT, USA) and PPL Therapeutics (Edinburgh, UK), genetic manipulation is currently being performed by researchers seeking to produce transgenic animals for organ transplantation. These animals have had human genes introduced into their systems in order to reduce the risk of complement activation and xenorejection, and the initial results appear promising.

Although there are various positions regarding the moral status of animals, it seems there will never be a clear-cut answer. Some, like physician-ethicist Peter Singer, view animals as having moral worth due to their capacity to experience pain and suffering. Singer argues that society takes the position of speciesism, namely, elevating the moral status of humans over that of animals, when instead, society should be considering animal suffering morally equivalent to human suffering. In Singer's view, animal experiments are justifiable only when we would consider using a human for the same experiment.⁸

Taking a utilitarian view, Singer posits that animals should only be used when the experimentation gives rise to more good than suffering. In research, it is impossible to always know in advance of the experiment what the outcome will be and we certainly cannot mathematically predict its good-to-bad ratio. Further, research does not usually benefit the subject at hand, but the information gained is rather for the benefit of future patients. It is unclear how anyone taking Singer's position can truly quantify and analytically balance pain, suffering, and medical benefit using human and animal models. These variables do not fit into tidy mathematical calculations, as Singer seems to suggest. Also, because humans are the ones conducting this balancing, the bias of the human cannot be ignored. Singer seems to place so many philosophical roadblocks before xenotransplantation that it is nearly impossible to ever remove them and arrive at the use of animals in medicine as being ethically permissible.

Taking an abolitionist view, philosopher and animal rights activist Tom Regan believes that all experimental medicine involving animals should be stopped.⁹ Regan sees these animals being used as only a means to an end, and that society fails to honor their basic right to be treated in ways that show respect for their independent value. Regan's abolitionist view is extreme; he seems to fail to realize that the life-saving medical technology that we possess today could not have been attained without the use of animals. Would Regan deny his children a life-saving porcine heart valve if they needed it? Would he choose to allow them to risk melanoma instead of wear-

ing chemical sunscreen (with a historical development using animal research)? I argue that there is no beneficence, but in fact, maleficence, if he denies his family these proven therapies. In my view, this maleficence would make denying his family these and other types of proven medical therapies ethically impermissible.

With xenotransplantation already posing ethical concerns, the addition of transgenic technologies adds even more fuel to the fire. The argument for viewing the genetic manipulation of animals as ethically permissible because genetic manipulation is already being performed on humans is undefendable. Most prominently, this argument speaks nothing to the key concept of genetic correction *versus* genetic enhancement. When speaking of human genetics and manipulation of the human genome, the intent is nearly always to correct a defect (with the aim of curing or preventing disease). On the other hand, when speaking of the genetic manipulation of animals, the focus is generally the enhancement of a 'healthy' genome. In this later case, there are no defects to be cured or prevented in the animal, but rather the animal is being modified for human use. In transgenic manipulation relating to xenotransplantation, for example, the animal genome is altered to facilitate the expression of human complement regulatory proteins on their organ surfaces in the hopes of preventing the organ from being recognized as foreign by the human body.

At onset, these statements make the transgenic manipulation of animals seem unethical, however, analyzing further, the story takes another turn. Whether manipulating the human genome to cure or prevent disease, or manipulating an animal genome to enhance it with human proteins, the motivation of both technologies is ultimately therapeutic. The ability of both technologies to provide clinical therapy is directly related to the ethical principle of beneficence. Does transgenic manipulation employ using animals as a means to an end? Yes, without question it does, but we use animals as a means to an end when we slaughter them for food, or for use of their skin to make clothing and baseball gloves. Which end (medicine, food, clothing, leisure activity) is ethical and who decides? If society finds it unethical to 'use' animals as a 'means' to the ends of curing disease and relieving human suffering, how can it justify the 'use' of animals for any human purpose? Whatever the moral claim of animals may be, I would be shocked if it allowed leather wallets and shoes, but disallowed organs for transplant.

A biological and ethical argument against xenotransplantation has focused on zoonosis. With the technology of xenotransplantation still emerging, the infection risk is still unclear. Endogenous retroviruses in porcine tissue have shown the capacity to infect human cells *in vitro*,¹⁰ with the FDA requiring retrovirus testing on xenotransplant recipients. In addition to the possible risk of animal to human infection, there is also the possible risk of human to human infection, with the route of infection also currently unknown. Not only could the transplant

recipient be risking infection in their own life, but they might also be risking infection to their immediate family, and possibly even society at large. Here the discussion then switches from autonomy to justice. Along with considering the possible benefits for oneself and others on the transplant list, we cannot forget our obligation to protect society from the spread of infection. If significant zoonosis theories are proved, the intended healing of the transplant community, would in fact be only temporary, and the technology would then be harmful to both the patient and others – thus making xenotransplantation ethically impermissible.

In conclusion, due to the unknown (and undeterminable) moral claim of animals, it seems unrealistic to attempt to use this concept as an argument against utilizing animals for medical therapy, even if it means modifying their genome. As medicine advances at what sometimes seems like lightening speed, it is important for society to make an ethical assessment of technology as it develops, instead of waiting for it to hit the marketplace. Emerging technologies need emergent ethical evaluation, as well as evaluation in the post-market phase in order to ensure the goals of medicine in current practice, while considering protection against future harms to society. In the event that the creation of transgenic animals proves to be an effective solution to the problems of limited human organs and xenorejection, and potential zoonosis risks can be combated, the ethical concerns of the technology should not be a barrier to its use, but they should be thoughtfully analyzed and re-visited by both scientists and society as a whole, as the technology progresses.

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