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*ANIMAL AGRICULTURE'S FUTURE THROUGH BIOTECHNOLOGY, PART 2*ANIMAL ORGAN DONORS:
HUMAN HEALTH APPLICATIONS

INTRODUCTION

The early years of the twentieth century brought a number of revolutionary advances in science and medicine. Of these, few equal the excitement and importance of vascular anastomosis, or surgical connection between two blood vessels. Vascular anastomosis permitted the repair of injured extremities, thus avoiding amputation and surgical penetration deep into body spaces. What especially gripped the imagination of surgeons, scientists, and the public 100 years ago, however, was that vascular anastomosis was the major technical advance needed for transplantation of organs to be considered in the treatment of disease (Guthrie 1912). Indeed, once developed, vascular anastomosis was applied immediately in experimental efforts in organ transplantation, and Alexis Carrel, an innovative surgeon, was awarded the Nobel Prize in medicine and physiology in 1912 for this work.

Although the surgical techniques needed to perform an organ transplant successfully were developed 100 years ago, two daunting barriers to clinical application remained. One barrier, not known then, was the need to suppress the immune system so that the organ would not be rejected. The other barrier, which was known, was finding a suitable source of organs to transplant.

Transplantation became feasible in the 1960s with development of immunosuppressive drugs that could be used to control organ rejection. With the rejection problem solved, at least in part, organ transplantation quickly became the preferred treatment for failure of the kidneys, liver, heart, lungs, and pancreas. But the problem of find-

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ing a suitable source of organs for transplantation was not solved so easily. In the early part of the twentieth century it was not evident that human organs could be available for this purpose, so xenotransplantation, the use of animals rather than humans as the source, was used in the initial attempts to treat organ failure by transplantation. In recent decades the ethical bar-

riers to using human organs have been overcome, but those organs are in short supply. For example, only approximately 5% of hearts needed for transplantation in human patients with heart failure become available (Figure 1); as a result, many people who need organ trans-

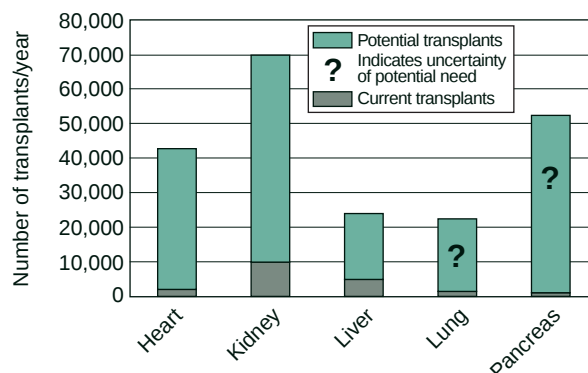


Figure 1. The actual number of transplants carried out in the United States each year and the potential number that could be carried out if sufficient human organs were available. Data obtained from Evans, Orians, and Ascher (1992). Recent studies confirm the need for organ transplants (Evans 2001).

plants must wait for extended periods of time. From 10% to 25% of those waiting for organ transplants may die before a human organ becomes available. Even this dramatic statistic understates the urgency of the problem, because many who die from organ failure are never placed on a waiting list for organ transplantation.

Because of this shortfall in available organs, transplantation does not begin to achieve its full potential for the treatment of human disease. A number of medical professionals continue to view animals rather than humans as the best source of organs, maintaining that by using animals as a source, the full needs of society can be met. This paper examines how xenotransplantation might be applied and describes barriers that stand in the way of that application.

APPLICATIONS FOR XENOTRANSPLANTATION

The most important human application for xenotransplantation, as previously suggested, is replacement of failing organs (Evans 2001). Figure 1 depicts the number of transplants actually carried out each year in the United States as well as the number that could be carried out if all organs needed were available. The need for replacement organs may increase even more than the figure indicates as the population ages, because the prevalence of cardiac failure and renal failure also will increase. In addition, the advent of genetic tests and other diagnostic tools to detect diseases such as cancer and organ failure at an early stage will make transplantation a potential means to preempt disease. The additional need for organs probably cannot be met by increasing the number of organ donors, which has been attempted previously without success; therefore, xenotransplantation is seen as one way to address this need.

Xenotransplantation also might be used to prevent the recurrence of diseases such as viral diseases that could afflict human, but not animal, organs and cells (Mueller, Davenport, and Ildstad 1999). For example, xenotransplantation has been proposed as a way to treat hepatitis, because hepatitis viruses can infect a human liver transplant but not an animal liver transplant (Starzl et al. 1993).

Another potential application of xenotrans-

plantation is as a means of “delivering” genes or gene products and complex metabolic pathways (Platt 1999). Genetic engineering of animals to gain expression of a gene could be a means of treating human disease if animal cells expressing that gene were transplanted. To the extent that an animal could be genetically engineered to express a certain protein or to metabolize a certain product, it might be preferable in certain circumstances to transplant the cells of animals that are suitably engineered rather than the cells of humans for this purpose. Finally, xenotransplantation could allow new “human” organs to be grown in animals for transplantation (Cascalho and Platt 2001b). In this sense, an animal could provide a biological environment in which human stem cells could be coaxed to form tissues and organs in ways that could not be countenanced for human subjects.

BARRIERS TO THE USE OF ANIMALS AS ORGAN AND TISSUE DONORS

If the potential applications of xenotransplantation are substantial, the barriers to application are equally so. The barriers include the immune reactions of the recipient with the graft, the possibility that animal tissues or organs might not function well in a human recipient, and the possibility that the xenotransplant might convey infections.

Of the barriers to xenotransplantation, the immune reaction of the recipient to the graft seems to be the most daunting (Cascalho and Platt 2001a). Xenografts provoke nearly every immune and inflammatory system, including the production of antibodies against foreign substances in the graft and the reaction of immune and inflammatory cells with a graft.

Among the immune and inflammatory barriers to transplanting organs between species, none is more difficult than that posed by the complement system. The complement system consists of a cascade of proteins in the blood, the main job of which is to attach to and destroy invading bacteria and viruses. In addition to this role, the complement system can attach to and attack cells of distant species. In the instance of porcine cells, the antibodies specific for swine cells trigger this attack. In fact, all normal humans have antibodies specific for

a sugar, Gal α 1-3Gal, present on cells from swine and other nonprimate mammals. The ability of the human complement system to destroy the cells of other species is amplified because natural controls of the complement cascade fail between species.

Genetic engineering has been used to address these problems (Platt et al. 1990). Human genes encoding the human complement control proteins have been introduced and expressed in swine (White and Wallwork 1993), and the gene encoding the enzyme that produces Gal α 1-3Gal has been disrupted (Lai et al. 2002; Phelps et al. 2003). These genetic manipulations may not suffice to allow xenotransplantation of organs, however. Immune reactions of a human against swine cells likely will extend well beyond the problems engendered by natural antiswine antibodies and the complement, and it is unlikely that these problems can be addressed in their entirety through genetic engineering. As severe as these immune and inflammatory reactions may be, the tools may exist to prevent or limit at least some of them.

The impact of immune and inflammatory reactions with the xenograft depends largely on the nature of the graft and the origin of blood vessels in the graft. Figure 2 illustrates this process in both organ transplants and cell or tissue transplants. Transplanted organs are subject to severe forms of vascular disease, including conditions known as hyperacute rejection and acute vascular rejection (Figure 3A). Hyperacute rejection refers to a condition in which an organ graft is destroyed in a period of minutes to hours—the most severe im-

mune-mediated condition known. Fortunately, hyperacute rejection can be averted by many different treatments and thus no longer is considered a severe impediment to successful application of xenotransplantation.

On the other hand, another type of rejection—acute vascular rejection—is a severe impediment that may be triggered by antiswine antibodies that recognize Gal α 1-3Gal. Recent efforts have focused on the development of genetically engineered swine that do not express this sugar. Although these efforts have received much attention, it is important to remember that the proteins of swine differ from the proteins of humans, and these differences may give rise to immunological reactions. Even if this genetic difference can be eliminated, many more remain, and immune reactions against xenografts and the suppression of immune reactions against xenografts will require the administration of immunosuppressive drugs for the rest of the recipient's life.

In contrast to organ transplants, cells such as liver cells and tissues such as pancreatic islets are much less susceptible to injury by immune responses (Figure 3B). These cells and tissues are less susceptible to immune-mediated injury because blood is fed to the organs through the recipient's blood vessels naturally grown into the graft, and the blood vessels of the recipient are not targeted by antibodies and the complement. In fact, studies in experimental animals and human subjects suggest that immune reactions against porcine cells and tissues may indicate that in the near fu-

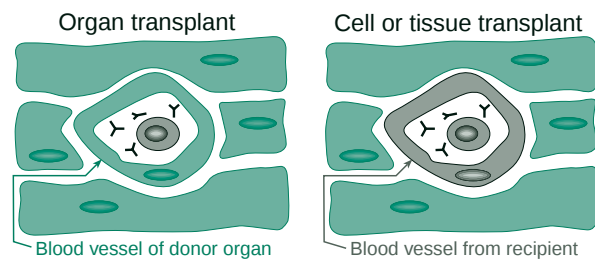


Figure 2. The origin of blood vessels determines susceptibility of xenografts to immunological attack. Organ transplants contain only donor blood vessels, which can be attacked via blood of recipients. Cellular or tissue xenografts contain blood vessels that grow in from the recipient, which are not attacked by the recipient's immune system.

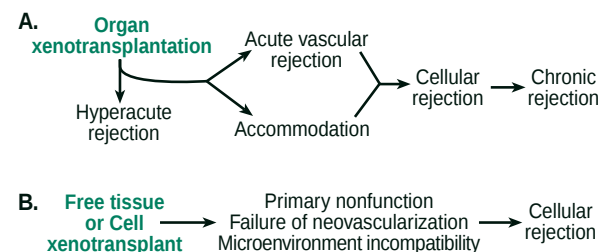


Figure 3. Biological hurdles for xenotransplantation. A. Organ xenotransplantation. B. Free tissue or cell xenotransplantation.

ture transplants of porcine liver cells (hepatocytes) and pancreatic islets will be conducted for the treatment of hepatic liver failure and diabetes, respectively. Because immunosuppressive drugs can control these immune responses, genetic engineering of swine may not be necessary for successful transplants of these cells or tissues.

Physiological Barriers to Xenotransplantation

Whether an animal organ or tissue would function in a human is a significant question for the field of xenotransplantation. Although the genetic differences between humans and animals are significant, and although these differences give rise to certain important incompatibilities, work to date suggests that most organs from animals—notably the heart, lungs, and kidneys—can work, provided they are not destroyed by the immune response. Even if the animal organ does not function perfectly, that organ may function better than the failing organ in the afflicted patient.

Significant concern exists, however, for the liver. Given the complex metabolic operations the liver performs, such as detoxification of substances in the blood and the production of proteins for coagulation and inflammatory cascades, the liver from swine or other animals might function inadequately in a human. But experiments conducted to date have shown intact livers and liver cells from swine to have a surprising capacity to correct metabolic defects associated with hepatic insufficiency and to provide adequate function. Hence, the concern may be unfounded. Furthermore, if the animal organ or tissue should function inadequately, there is the possibility that genetic engineering could be applied to improve that function.

Infection as a Barrier to Xenotransplantation

The possibility that a xenograft might transmit an infection from the animal source to the recipient has received much attention in recent years (Chapman et al. 1995). The transmission of infection is an occasional problem in human-to-human transplants because organ donors cannot be screened fully before the transplant procedure. In principle, animals can be screened fully, and therefore this problem should be rare. But screening of

source animals cannot avert all infections. Certain viral elements already exist in the genetic makeup of the animal; these elements are referred to as endogenous retroviruses (Patience, Takeuchi, and Weiss 1997). Although these elements cannot be eliminated by screening for absence because they are present in all swine, it may be that certain families of swine cannot transmit these viruses to human cells in vitro. Concern exists, however, that this virus, or viral genes, in a human recipient could spread to other humans.

Whether such an event might occur has been the subject of investigation in recent years, and thus far no evidence of transmission in vivo has been detected. Still, this concern has provoked careful monitoring of human subjects who have received experimental xenografts and undoubtedly will increase on-going efforts to detect viral transmission in the future.

GENETIC ENGINEERING OF ANIMALS FOR TRANSPLANTATION

One aspect of xenotransplantation that has stimulated much excitement and discussion is genetic engineering. Genetic engineering is viewed as a way to modify animals so that genes potentially could be added to or disrupted in a line of animals, the organs or cells of which might be used for xenotransplantation. At present, genetic engineering is viewed as a way to modify a line of animals so that their organs and cells would be less likely to provoke an immune response, making those organs or cells more acceptable to a human recipient. As previously suggested, however, genetic engineering also might be undertaken to add new physiological properties to the transplant or to avert physiological limitations. Genetic engineering also might be undertaken to eradicate an endogenous virus or viral genes to permit safer application of xenotransplantation in human subjects.

The full extent of genetic engineering required for the production of swine for transplantation is not known and may require the addition of new genes as well as the modification of genes already present in the swine genome. The addition of a gene(s) has been possible in many species for several years, and many genes have been added to swine for the purpose of decreasing immunorejection.

Unfortunately, the major barrier preventing a better understanding of rejection after xenotransplantation has been that of hyperacute rejection. Hyperacute rejection is caused by natural (or preformed) antibodies that recognize the transplanted tissue. In the instance of swine tissue, this foreign molecule is a Gal α 1-3Gal linkage on the cell surface. Because primates have natural antibodies (likely generated in response to exposure to bacteria that have the Gal α 1-3Gal on their cell surface) that recognize the Gal α 1-3Gal, the best course of action is to remove the Gal α 1-3Gal from the cell surface of the swine tissues. The only way that this removal can be accomplished completely is to disrupt the gene responsible for making the enzyme that catalyzes the addition of a Gal α 1-3Gal linkage. The gene is α 1-3galactosyltransferase, and it is present as a single copy in the swine genome.

In mice, the disruption of a gene such as this has become routine. The technique in mice involves the use of embryonic stem cells and homologous recombination. Unfortunately, despite considerable effort by researchers, embryonic stem cell technology has not been developed for any other species; thus another methodology is required to make a modification to an existing gene in the swine genome.

The two technologies that came together to make a genetic modification to an existing gene in swine are homologous recombination and nuclear transfer. Homologous recombination, similar to crossovers that occur normally during meiosis, can be used to make the specific genetic modification in cells such as fetal-derived fibroblast cells. These cells are relatively easy to acquire and have considerable capacity to proliferate in vitro. The ability to divide many times in vitro before undergoing senescence (becoming old) is important because it provides (1) the cell divisions necessary to select only those cells that have undergone successful homologous recombination and (2) a chance to grow these clones to a stage in which vials containing 500 to 1,000 cells can be frozen. These vials then can be thawed and used for nuclear transfer or cloning procedures.

Nuclear transfer procedures were developed in domestic animals in the 1980s and applied to fetal

and adult cells in the 1990s (Campbell 2002). The procedures involve taking a mature egg and removing the metaphase chromosomes. The nucleus from the genetically modified cell then is introduced into the cytoplasm of the egg by direct microinjection or by cell fusion. The egg then is activated or stimulated to behave as though it was fertilized, so it begins to develop. It is thought that cytoplasmic proteins in the egg then associate with the nucleus and cause it to be restructured such that it is reprogrammed. The nucleus then is “reset” to begin the developmental process as in a normally fertilized egg.

These nuclear transfer procedures generally are successful less than 1% of the time. In addition, many developmental anomalies occur, likely the result of incomplete reprogramming of the genome or incomplete epigenetic reprogramming. Because much of the epigenetic program (e.g., DNA methylation) gets reset during gametogenesis (the production of gametes), these developmental anomalies seem not to be passed on to subsequent generations. Thus, any developmental anomalies that result from the cloning procedures are a management concern only in the first generation. If the founder animals reach puberty and then reproduce, the genetic modification made to the fibroblast cells is integrated stably into the genome of the offspring (Prather et al. 2003).

SELECTION AND BREEDING OF SWINE FOR XENOTRANSPLANTATION

In addition to the intentional introduction or elimination of genes by genetic engineering for xenotransplantation, swine or other animals might be bred specifically for this purpose. Certain researchers have suggested that a line of swine—miniswine—might be used because their organs are more suitable in size for use in humans than organs from most domestic lines of swine. Breeding also might be undertaken to eliminate viruses. Finally, it is possible from a theoretical perspective that swine might be bred to have a decreased capacity to stimulate an immune response because of the histocompatibility antigens they express, or that swine might in some way be “matched” with a human to minimize immunological reactions.

ETHICS OF XENOTRANSPLANTATION

The use of animals as a source of cells, tissues, and organs for transplantation has raised ethical questions. Certain of these questions stem from the “use” of animals for the benefit of humans. This concern, although discussed widely, has not prevented consideration of xenotransplantation for clinical application and experimental trials. Those discussing this subject often have concluded that societies that countenance the use of animals for labor or as a source of food could not as a matter of policy abjure the use of animals as a source of transplants.

Another question, one that has limited the clinical application of xenotransplantation, is whether a xenograft might transmit an infectious organism from that animal to the human and then spread in the human population. This question leads one from a scientific perspective to an ethical question of how the risk to the human population as a whole should be weighed against the potential benefit of xenotransplantation to the individual.

At the present time, no microbial agent has been identified that can be passed to a human exclusively by xenotransplantation. Thus all microbes of the pig, such as swine influenza, known to be capable of being transmitted from animals to humans would enter the human population whether or not xenografts were performed. On the other hand, there is a small theoretical possibility that a new organism could form as a result of recombination of human and animal or viral genes (Ogle et al. 2004). This possibility is focused particularly on the porcine endogenous retrovirus (Patience, Takeuchi, and Weiss 1997). Studies to date have not revealed any cases in which new agents involving porcine endogenous retrovirus have formed, except in an experimental model system in which human cells were transplanted into swine (Ogle et al. 2004). Although this risk is only theoretical, it is carried by the public; therefore, performing xenografts is viewed as weighing individual benefit against a small public risk, and striking this balance is viewed as a matter of ethics.

What has not received due consideration is the possibility that xenotransplantation might confer a benefit to the public, such as the opportunity to

identify new and emerging infectious agents or the means by which large numbers of people could be treated, and this benefit should be weighed against the small risk of a spreading infection. The subject has been addressed by the Institute of Medicine (1996) and the U.S. Food and Drug Administration (2001) in the United States, as well as by public agencies abroad.

PROSPECT FOR USE OF ANIMALS AS ORGAN AND TISSUE DONORS

Xenotransplantation is one of several technologies (e.g., stem cells, tissue engineering, and implantable devices) that might be used for the treatment of human disease. Xenotransplantation of organs offers the advantage that the physiological performance of the graft is roughly similar to that of normal human organs. Xenotransplantation of organs is hindered, however, by the severe types of vascular disease discussed previously. Cell and tissue xenografts are not susceptible to a severe immunological barrier, but with the possible exception of pancreatic islets, cell and tissue xenografts do not offer the full physiological competence of intact organs.

Despite the challenges posed by the barriers to xenotransplantation, it is possible to envision compelling and exciting applications. Certain xenogeneic cell and tissue transplants might well be undertaken today. Porcine hepatocytes might be transplanted for the treatment of cirrhosis caused by hepatitis viruses. The advantage here is that the xenogeneic hepatocytes would not be susceptible to infection by the virus, and the introduction of those cells is far less invasive than a whole-liver transplant. Similarly, xenogeneic islets might be used in lieu of pancreas transplants to treat certain patients with diabetes. But whether these types of transplants and the immunosuppression needed to support them would outweigh the risks of this treatment remains unclear.

One possible interim application in the application of xenotransplantation might be the use of swine organs as a “bridge” to transplantation with a human organ. This application would not address the shortage of human organs, because a human organ transplant still would be conducted, but it

would provide important information about whether the immunological barriers to xenotransplantation had been addressed adequately. At present, this question is addressed by experiments using nonhuman primates as recipients of xenografts; these experiments are hindered, however, because certain genetic manipulations in swine as well as the drug therapies used are designed for human recipients, not for nonhuman primates. If bridge transplants show sufficient promise, it is possible to envision the eventual application of transplantation of porcine organs for the treatment of organ failure. How these transplants would compare in their function and complications against alternative technologies remains unclear. Xenografts might be used for the treatment of pulmonary failure because no other options exist and human lungs are in short supply. On the other hand, xenotransplantation might be less applicable for the treatment of cardiac or renal failure because implantable devices and dialysis might be adequate alternatives.

Still remote is the very exciting possibility that someday animals might be used as a system in which human organs and cells can be grown. This may be the ultimate way in which xenotransplantation can impact human health.

ADDITIONAL TOPICS IN THE SERIES ANIMAL AGRICULTURE'S FUTURE THROUGH BIOTECHNOLOGY

The CAST Board of Directors approved a series of issue papers on this topic. Part 1, *Biotechnology in Animal Agriculture: An Overview*, was published in February 2003 as Issue Paper 23; the current paper is Part 2. Other titles will follow:

- Animal Productivity and Genetic Diversity: Transgenic and Cloned Animals
- Food and Feed Safety of Biotech Crops Fed to Livestock: Safety of Human Consumption of Milk, Meat, and Eggs
- Metabolic Modifiers for Use in Animal Production
- Role of Biotechnology-derived Animals in the Development of New Medications for the Treatment of Human Disease
- Vaccine Development: Recombinant DNA

Technology for Animal Health and Food Safety through Microbial Genomics

- Environmental Impacts of Biotechnology-derived Crops on Animal Manure Nutrient Management
- Ethical Perspectives on Animal Biotechnology

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Additional copies of this issue paper are available for \$5.00. Linda M. Chimenti, Managing Scientific Editor. World Wide Web: <http://www.cast-science.org>.

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