Xenotransplantation

An Honors Thesis (HONRS 499)

by

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This is a presentation on xenotransplantation, which is the transfer of organs or tissue between two different species. This area of scientific research is making significant headway in the world of transplantation and may save thousands of lives in the near future. An explanation of what xenotransplantation is and what it must overcome in order to be successful is the starting point of this discussion. Following this introduction, is a discussion of the latest research in xenotransplantation and the knowledge gained through each study. The concerns of the risks involved are also addressed with varying views of where xenotransplantation is headed. In the hopes of reducing risks and allowing the research for cross-species transplantation to continue, the presentation ends with the regulations set forth by the Public Health Service.
Xenotransplantation

Due to the advancements in medical research and technology, organ transplantation has become an accepted and successful practice. The latest technology has come so far that there are tens of thousands of people in the United States every year waiting for new and healthy organs. The biggest problem faced by these people in need and by transplantation surgeons nation wide is that there are not enough human organ donors available. In 1996, there were 33,000 people in need of an organ transplant and nearly 3,000 of them died because there were simply not enough donor organs (Benowitz 1996). In an attempt to find a solution to this shortage, research scientists have looked into a different kind of donor for transplantation, one of a different species than the Homo sapien. Xenotransplantation, the transplantation of tissue or organs between different species, has gained a new importance in medicine today and has made some major leaps in the last three years. Although there has not been a successful xenotransplant yet, immunologists have made significant headway in understanding what is involved in xenotransplant rejection and survival and the risks involved in transplanting tissue or organs from one animal to another.

Much like dealing with allograft transplantation (transplantation between the same species), xenotransplantation must overcome rejection. Hyperacute and acute rejection are two important processes involved in destroying a transplanted organ. Hyperacute rejection occurs over the short period of time of a few minutes to a few hours and involves the destruction of the transplanted organ by preformed antibodies in the recipient to the
donor's antigens that activate the complement system. This complement system causes
the activation of platelets, thrombosis, endothelial injury and fibrinoid necrosis that leads
to rejection (Benjamini 1996). In hyperacute xenograft rejection, endothelial
glycoproteins have been identified as targets of these antibodies and complement.
Specifically, the alpha-galactosyl epitope expressed on the cell surfaces of all mammals
excluding the Old World Primates has been observed (Rother 1996). The Old World
Primates have anti-Gal that recognize the xenoantigen of alpha-galactosyl and creates a
natural immunity by activating the complement system. Acute rejection, unlike the
humoral immune response of hyperacute rejection, is a cell mediated immune response
involving T-cells. This form of rejection includes a heavy infiltration of lymphocytes and
macrophages into the transplanted organ that eventually destroy it. This is often seen
when the donor recipient has not been previously sensitized to the transplanted organ
(Benjamini 1996).

Included in the rejection of xenotransplants are the different types of animals
involved in the transplant. How closely the animals are genetically related plays a critical
role in the response of the host and donor to each other. There are two basic types of
xenotransplants. Those of concordant type are transplants of organs between species that
are closely related. The rejection observed in this type of xenotransplant is not as dramatic
or as fast as rejection seen with more distantly related species. Concordant
xenotransplantation can be further divided into easy and difficult transplants according to
rejection process severity. Rejection during easy concordant xenotransplantation is similar
to rejections seen in allograft transplantation. The most important antigens causing
destruction of the organ are histocompatibility antigens and specific xenoantigens present of the organ. Difficult concordant xenotransplantation shows the most significant antigens are the glycoproteins that have the alpha-galactosyl epitope. Large amounts of antibodies are produced by the host in response to the xenoantigen and rejection occurs after a few days. The other type of xenotransplantation, discordant transplantation, involves species that are not closely related genetically. This form of rejection occurs within minute to a few hours and it is extremely dramatic. The activation of the classical and the alternative pathways of complement are the major components of this form of rejection.

Each of these types of xenotransplantation has particular obstacles to overcome in order to stop rejection from occurring. Easy concordant xenorejection can be interrupted by immunosuppressive drugs such as cyclosporin and other anti-proliferative substances (Kemp 1996). Difficult concordant xenorejection has been shown to be reduced by the use of immunosuppressive substances aimed at prevention of newly formed or possible future xenoantibodies from being formed. Such substances include cyclosporin, FK-506, leflunomide, rapamycin, brequinar sodium, cyclophosphamide or cobra venom factor (Kemp 1996). Discordant xenorejection can be blocked by inactivating the complement system and/or by using transgenic animals with a complement system that has been altered. Complement can be inactivated by using soluble complement receptor type 1 (SCR 1) which becomes bound to and inactivates the C3 and C5 convertases of the classical and alternative complement pathways (Bollinger 1996). In transgenic animals, the human regulatory proteins of DAF, MCR and CD59 of complement are incorporated into the donor animal for resistance to hyperacute rejection (Bollinger 1996).
Not only is understanding the mechanisms involved in the different types of xenotransplantation rejection important, but other factors become critical in determining what animals are the best suited for transplantation. Concordant xenotransplantation may be easier to control, but it has many disadvantages. Animals that are more closely related to humans, such as chimpanzees, are not available in large numbers, they are slow to reproduce, and may carry pathogens that could infect humans. Discordant xenotransplantation may be more difficult to control, but it has many advantages. Animals that are not closely related to humans genetically such as pigs are available in large numbers, they come in different sizes, they reproduce quickly, and they have only a small number of pathogens that could infect humans. Pigs can also be easily manipulated through genetic engineering (Bollinger 1996).

Considering hyperacute and acute rejection, concordant and discordant species, and humoral and cell mediated immune responses, researchers have devoted much time and energy to find a way to succeed in xenotransplantation. Within the past three years significant progress has been made through the study of several different types of xenotransplantation attempts. Important combinations of animals that have been key to better understanding this cross-species transplantation are pig-baboon, guinea pig-rat, human-rat, pig-dog, human-mouse, rat-mouse, human-baboon, and hamster-rat.

In the study of xenotransplantation between pigs to baboons, several key mechanisms for rejection were examined as well as possible methods to prevent it were explored. In one study, researchers used pigs and baboons to examine naturally produced antibodies specific for xenoantigens (Bailey 1994). These antibodies are responsible for
activation of the complement system which leads to hyperacute rejection. Pig hearts were transplanted into baboons and the natural antibodies produced against pig white blood cells, pig red blood cells, and pig endothelial cells were to be measured and observed for their role in the hyperacute rejection. The researchers attempted to stop these antibodies from promoting the complement cascade by several methods. They attempted to adsorb the baboon's natural antibody from several organs of the baboon. The pig heart in the baboon showed prolonged survival with the antibody absorption (Bailey 1994). The scientists also attempted to decrease the natural anti-pig antibody in the baboon by performing a cardiopulmonary bypass which dilutes the blood. Dilution of the blood was successful at reducing the anti-pig antibodies found in the baboon and indicates that the decreasing of the anti-pig antibodies against red blood cells could contribute to the prolonged survival of the pig heart in the baboon.

Pigs and baboons have also been used to study the idea of possibly using xenotransplantation as a means of keeping someone alive until a proper allograft is available. The idea of using cross-species organs as a bridge brought up the question of whether or not using a xenograft first would increase the chances of quicker cellular rejection as well as humoral rejection due to the sensitization of the recipient by the xenograft. In this study they tested baboons by first transplanting a pig heart into the baboon and then following the xenotransplant with an allografted transplant (Baker 1995). The survival of these allografts were observed. The results of this research showed that the primary pig heart in the baboon did not lead to the sensitization of the baboon to the secondary baboon heart. The allografts appeared to functional as normal and there was no
indication of hyperacute rejection or cellular rejection of the transplanted heart.

The combination of guinea pig and rat in xenotransplantation models has also lead to the further understanding of rejection and the possibility of inhibiting of it. There has been a study with these two animals to explore the part that phosphatidic acid plays in xenotransplant rejection. Phosphotidic acids play a key part in intracellular signaling and are observed to be activated at the time of the inflammation response. The chemical substance of lisofylline acts to inhibit this critical role of phosphatidic acid and thus slows down or stops the inflammatory response. In this study, guinea pig hearts were transplanted into rats. Two particular drugs were tested to see if they could inhibit the inflammation caused in xenotransplant rejection by stopping the activation of phosphatidic acid. The drug of methyprednisolone (MPS), which is a steroid, had a small effect on the prolonging of the survival of the guinea pig heart in the rat (Fung 1996). Lisofylline used by itself had a larger effect on the survival of the heart than the MPS, but the two drugs used together in this study showed a significant increase in the length of survival of the transplanted organ (Fung 1996).

Another study using guinea pigs and rats that contributed to the better understand of long-term survival of xenotransplants in animals distantly related, genetically. In this study, splenocytes were tested to see how they were involved in the hyperacute rejection of xenotransplantation. The splenocytes of guinea pigs were injected into the spleens of rats. Certain immunosuppressive drugs were used to test for their effect on the prevention of rejection. It was observed that the splenocytes of the guinea pig were responsible for activating both B cell and T cells of the rat's immune response. The research team found
cyclophosphamide and FK 506 to be successful chemical substances that act to decrease the activation of T cell and thus able to prolong the survival of xenografts (Hayashi 1994).

Guinea pigs and rats have also been used to explore the effects of particular synthetic drugs on the rejection of discordant xenotransplants. The drugs used in this case were sulfated oligosaccharides types A and B. They were tested to find their possible role in the inhibition of endothelial cell activation which is a major component in the hyperacute rejection process. The exposure to these oligosaccharides just before revascularization led to an increased length of the xenograft survival. The saccharides were observed to prevent the release of heparan sulfate from the cardiac endothelial cells of the guinea pig that would normally be induced by the rat serum (Buler 1996). This heparan sulfate is located on the surface of endothelial cells and plays a significant role in many of the physiological properties of the blood vessels such as preventing thrombotic cell surfaces, injury from oxidants, and the flow of plasma proteins and blood cells out of the vessels (Buler 1996). In the process of hyperacute rejection, antibodies (IgM) bind to the endothelial cells and this interaction activates complement. This activation of complement in turn causes heparan sulfate to be released, causing the major features of the pathological rejection. Both oligosaccharides A and B were observed to prolong the life of the xenograft between two distantly related species. This can be an important advancement in other xenotransplants as well. Oligosaccharide A has been observed to inhibit the heparan sulfate release in humans also (Buler 1996).

Human to rat xenotransplantations have also been important in the building knowledge of this transplantation. In one study using humans and rats, the possibility of
the induction of tolerance to foreign cells was determined. Knowing that the rejection of this type involves both humoral and cellular mechanisms, the researchers injected islets and bone marrow in distantly related animals in hopes of controlling these mechanisms. They wanted to test the possibility of prolonging the life of human islets transplanted into the kidneys of rats following the injection of the thymus of the rat with human bone marrow. This bone marrow injection is an attempt to induce tolerance of the rat to human cells. Since earlier studies had shown that this sort of tolerance induction to be successful in allograft transplantations, it was a disappointment to find that this xenograft transplant did not produce the same success. The treatment of the rats with human bone marrow did not produce a significant tolerance that was able to prolong the survival of the islet xenograft (Castagna 1994). Almost as important as successful trials in xenotransplantation, failures to lengthen life of xenografts are extremely important in furthering the understanding and possibilities of the mechanisms in cross-species transplantation.

Another success story in xenotransplants is a study done with pigs and dogs. In this investigation, hyperacute rejection and the problem of preformed antibodies against donor organ antigen is further explored. The researchers attempted to remove the antibodies from the recipient through different means in order to study the nature of this hyperacute rejection. In this case, pig kidneys were transplanted into dogs. It was observed that having low levels of xenoantibodies led to increased survival of pig kidneys (Davies 1994). The removal of the anit-pig antibodies from the dog involved different forms of adsorption. This adsorption was done by removing plasma from the dog and pouring the plasma through a specific donor organ and then returning this plasma back
into the dog. One case of adsorption was done with pig spleen and it removed about 92% of the anti-pig antibodies. Adsorption was also done with pig liver. The liver was used because it had a greater surface area of endothelial cells. This process was successful at removing about 98% of the xenoantibodies. The research team went further in their attempt by first using the pig spleen to adsorb the anti-pig antibodies and followed it with another adsorption using pig liver. Again, 98% of the xenoantibodies were removed (Davies 1994). After the completion of the adsorption process, the pig kidneys were placed into the dogs and the results recorded. In the normal hyperacute rejection without the adsorption of xenoantibodies, features such as vascular microthrombi, mild infiltration of polymorphonuclear cells, and interstitial edema was seen. After the adsorption of the preformed anti-pig antibodies, the features of hyperacute rejection showed no evidence of microthrombi, but did show tubular necrosis, interstitial edema, and infiltration of neutrophils (Davies 1994). In untreated dogs, there was also observed heavy deposits of IgG and IgM of particular patterns in the spleen. In dogs that had undergone treatment of xenoantibody adsorption, the deposit of IgG and IgM were not as heavy although the patterns were still the same. This study concluded that the reduction of preformed xenoantibodies can prolong the survival of the xenograft and it is possible to significantly reduce the level of xenoantibodies although not completely (Davies 1994).

The interaction of cells between two different species has not always been studied for the purpose of seeking a means of prolonging the survival of an organ or tissue. In one study, humans and mice were used to study apoptosis and its role in fighting tumors. This programmed cell death is initiated by natural killer cells, T cells, and cytokines. It has
been observed that an AOP-1 antigen can be located on the surfaces of activated T cells and B cells. When the murine antibody binds to this AOP-1 antigen, programmed cell death is activated. The presence of an anti-AOP-1 antibody could play a role in the destruction of cells expressing this AOP-1. It was observed that the anti-AOP-1 antibody is a mediator of cell death. Unlike complement or antibody-dependent, cell-mediated cytotoxicity, it does not require effector cells. By binding the F(ab')2 fragments of the anti-AOP-1 antibody programmed cell death was inhibited. This indicates that the anti-AOP-1 antibody could play a role in the killing of tumor cells (Coney 1994). The combination of mouse and human antibodies were made of the anti-AOP-1 type with the human isotype of IgG3 to test their effectiveness at initiating apoptosis. This chimeric antibody was seen to play an important part of programmed cell death of tumor cells that express the AOP-1 antigen (Coney 1994). This research is important because the ability to produce antibodies for specific tumor cells could lead to needed anti-tumor reagents. This study showed the possibility of making an anti-AOP-1 antibody that has a decreased immunogenicity (due to the human Fc region) but does not alter the antigen's ability to bind to target cells. It is also possible to cross-link this anti-AOP-1 antibody with AOP-1 antigen to cause a regression in tumors. This antibody is especially important for the fact that even low levels of this anti-AOP antibody can cause the regression of large tumors (Coney 1994). This study could be important in xenotransplantation in furthering the knowledge of chimeric molecules and their role in making an antigen "less foreign" and thus less likely to cause rejection of donor tissue or organs.

Mice have been used in many other studies in xenotransplantation. There have
been several cases involving transplants between mice and rats. One important exploration focused on the role of MHC class I and II molecules in the acceptance or rejection of xenotransplantation. MHC molecules are key players in recognition of xenoantigens and induction of the activation of effector cells. A study of this role was done through the transplantation of liver and hearts from MHC class I and II "knock out mice" into rats. These donor mice had the self recognition cell surface markers removed before the organ was transplanted. Rat livers and hearts were also transplanted into these types of mice. The results of these xenotransplantation indicate that the rejection of the rat heart in the mouse recipient showed infiltration of mononuclear cells and heavy thrombosis. The mouse liver and heart in the rat revealed humoral responses were primarily involved in this rejection. This study suggests that the MHC class I and II molecules of the donor may be of little significance in the tempo of xenograft rejection between these two species (JJ Fung 1996).

Another study involving rats and mice takes the previous observation concerning the MHC molecules and tests another mechanism effecting the tempo of xenograft rejection. Since the MHC class I and II "knock out" recipients showed no change in the tempo of rejection, direct presentation of the xenoantigen by the donor's antigen presenting cells were suspected. This was examined through the use of the hearts of mice that have been injected with the bone marrow of the recipient before being transplanted into rats. This was done to attempt to induce tolerance. The outcome was a slight increase in xenograft survival (Denetris 1996). The experimental procedure was extended by the addition of the drug FK 506 with the bone marrow. This showed a much more
significant prolonging of heart survival. When these transplanted hearts were studied for
the movement of cells of both the donor and recipient, the chimerism showed that 50-
90% of the cells were those originating from the donor. This indicates that the donor
leukocytes may be critical in the recognition of the xenoantigen in concordant
xenotransplantation (Denetris 1996).

The search for successful transplantation between rats and mice continues on to
yet another study. This one focused on the role of antibodies in the acceptance and
rejection of xenotransplants. The key players involved are the chimeric molecule of
CTLA4Ig and anti-CD4/CD8 antibodies. The activation of T cells through the TCR is
costimulated by the interaction of CD28 with its B7 ligand. Thirty two percent of the
amino acids of the CTLA4 are identical to the CD28 and CTLA4 is a co-receptor for B7.
The genomic organization of the two are also similar. The CTLA4Ig has been observed to
stop the production of T cell dependent antibodies, thus preventing the activated T cell
proliferation. Other proteins, anti-CD4 ant anti-CD8 antibodies, were used to test for
their ability to prolong the survival of xenotransplants. The treatment of anit-CD4/CD8
antibodies and CTLA4Ig of the donor skin and heart before transplant was attempted
between rats and mice. GK1.5 is the specific antibody that limits the proliferation and
lymphokine release of CD4. GK2.43 is the rat antibody (IgG) that targets CD8. The anti-
CD4 antibody was observed to cause the longer survival of transplanted hearts indicating
that CD4 plays an important role in the rejection of xenografts. Anti-CD8 appeared to
have no effect on the xenograft rejection by itself (Flye 1996). Using these antibodies, the
research team used different combinations to observe their effects on the rejection. The
combination of GK1.5 and GK2.43 showed a prolonged survival of the transplanted organ. CTLA4Ig by itself also prolonged the survival and when it was combined with the other two antibodies the xenograft survival was significantly extended (Flye 1996).

A study involving hamsters and rats has lead to an important growth of knowledge for xenotransplantation. With all the advancements made in stopping hyperacute rejection there is still another problem transplant specialists must face. When hyperacute rejection is successfully avoided, the xenograft is rejected even with the use of high levels of immunosuppressive drugs. This rejection is referred to as delayed xenograft rejection. This type of rejection involves the ineffectiveness of immunosuppressive drugs, large amount of xenoantibody deposition, the infiltration of cells consisting mainly of macrophages. The effector cells that play critical roles in this form of rejection are a combination of antibodies, macrophages, and natural killer cells. Hamsters hearts were transplanted into rats to study this delayed xenograft rejection. Hyperacute rejection was inhibited by the combination of the immunosuppressive drugs of leflunomide and cyclosporine and this delayed rejection was observed. When the immunosuppression was withdrawn, the xenograft was rejected within 6-11 days. This was paralleled with an increase in the number of antibodies produced and cellular movement into the donor organ (Chong 1996). This study showed its importance in the fact that it brought to the awareness of others that overcoming hyperacute rejection is only the first step in performing a successful xenotransplantation.

One of the most recent as well as controversial studies that has taken place in the U.S. is the transplant between baboon and human at the University of California in San
Knowing that baboons are resistant to the HIV virus and that there have been no natural antibodies found in the human immune system that are specific for baboon antigens, transplant surgeon Suzanne Ildstad sought the approval to transplant the bone marrow of a baboon into a patient suffering with AIDS. Jeff Getty, the AIDS patient, was successfully given the baboon bone marrow in December of 1995 after a severe pretreatment of large doses of anti-rejection immunosuppressive drugs, chemotherapy and radiation. As of October of 1996 Getty seems to be healthy. His T cell count is at 75 cells per square millimeter of blood. This is the highest his T cell count has been in four years and it is four times the count as when he began the transplant procedure (Benowitz 1996). Although Getty is improving, there is no evidence that it is due to the baboon bone marrow. The studies are still being done to see in the bone marrow took in Getty. If the bone marrow took, baboon lymphocytes will be present in lymph tissue of Getty. Ildstad is optimistic, however, and she is already in the process of seeking approval by the FDA for another baboon bone marrow transplant into human with AIDS.

In Ildstad's hope of successful xenotransplantation, she has recently moved to Allegheny University where she is head of the newly formed Institute for Cellular Therapeutics. The goal of this organization is to bring together people from all necessary areas of science to bring about this success. It includes transplant surgeons of organs and bone marrow, immunologists, and molecular and radiation biologists. Ildstad plans to address several issues which involve the use of bone marrow in inducing tolerance in xenotransplants, the use of targeted cell therapies to fight opportunistic infections, and to examine the use of bone marrow transplants in combating autoimmune diseases.
The University of Pittsburgh is another leading resource in the growing knowledge of transplantation. Through several extensive laboratory studies, they have determined four drugs that are most successful in xenotransplants involving humans. These drugs include cyclophosphamide, FK506, prednisone, and prostaglandin E (Rossi 1996).

Cyclophosphamide is a chemical substance that prohibits the proliferation of B cells. The function of FK506 is to interfere with and inhibit the T cell of the recipient from destroying the donor organ. The steroid hormone prednisone plays a role in inhibiting the activity of antigen presenting cells and prostaglandin E manipulates cytokines and other cell that induce inflammation.

With all of these advancements in xenotransplantation, there are many people who are against the furthering of this research for several reasons. Their biggest and most compelling argument is the possibility of animal viruses infecting humans. With the unpredictable mutations of viruses and the ability of these viruses to recombine with other pathogens, dangerous new diseases could arise. The recipient of the animal organ donor would be at high risk because their bodies would not be able to fight these new pathogens due to the high doses of immunosuppressive drugs that the patient would be given to help them to prevent rejection of the donor organ. This infectious virus could even possibly be passed on to all of the people who come in contact with the xenotransplant recipient. This could possibly lead to a pandemic that could reach the entire globe (Koechlin 1996).

There have been several cases of such animal viruses causing severe illnesses and even death in the human population. In 1967 there was an importation of monkeys into
Germany that were infected with Marburg filovirus. This virus found hosts in humans and 31 people were infected and 23% of those infected died. Sudan (in 1976) and Zaire (in 1976, 1979, and 1995) both experienced such a virus, the Ebola filovirus, that had a case fatality rate of 80-90%. The Crimean-Congo hemorrhagic fever virus jumped from a goat to humans in Pakistan in 1976. This virus infected 17 people with a fatality of 24%.

Another important case which involves HIV is one of speculation. The HIV viruses type 1 and 2 are suspected to have originated from a monkey that passed the virus to humans (Koechlin 1996).

Another argument for the opposition to xenotransplantation is the fact that the risks of this form of transplantation is largely unknown. "Too little of the science behind the experiment is understood," said virologist Jonathan Allen in his skepticism of this type of transplantation. Others are arguing the fact that even with carefully designed tests, there cannot be a test to screen for something that is unknown (Hanson 1996). The unknowns can also expand into the effect that these animal cells would have in the human body and most importantly to the human mind. With part of the body of human origin while other parts of another animal origin, it could change world's ideas of what it is to be human (Koechlin 1996). There is a possibility that xenotransplantation could affect the recipient's identity and sense of self.

The research scientists behind these studies as well as others are quick to the defense of xenotransplantation. They do not feel that the risk to an infectious disease being transmitted between animal and human is a very large risk. The Secretary General of a Swiss pharmaceutical lobby group, Thomas Cueni, believes that there is only an
extremely small chance of finding pig viruses that would be dangerous to humans (Koechlin 1996). In rebuttal to the fear of mutations and recombinations of viruses, it was said at the Institute of Medicine conference in June of 1995 that these researchers "are doing nothing different from what is already occurring in nature. In fact, nature is more dangerous because the genetic mutations occurring in nature are not controlled, as they are in the lab." With the careful controls of the laboratory this procedure could be eliminated of many of the risks of concern. In response to the human identity being lost, xenotransplant advocates feel that this would not be an issue. The humanity of the recipient is protected by the blood-brain barrier which would not allow the animal cells to cross over into the brain.

One of the biggest arguments in support of xenotransplantation is the indisputable need for organs. As mentioned before, approximately 33,000 patients are on the waiting list for an organ and its is expected that nearly half of them will die before a proper organ is found for them. Not only are solid organs in need, but so are tissues and cells. One million people in America will die of AIDS in the next seven years. The possibilities of Ildstad's baboon bone marrow in human AIDS patient study could save many lives. Jeffrey Platt of Duke University supports xenotransplantation on the base of need by saying that with the shortage of organs and the tremendous clinical need for them, the medical profession has the ability to help those in need but not enough organs. Xenotransplants could give the organs needed to save thousands of lives.

The fact that using animals to successfully aid humans has already being done is another compelling argument for the pro-xenotransplant side. There are many instances
everyday in which biological material is taken from animals and is placed in humans. Such examples include the use of fetal calf serum, calf serum, and horse serum that are used in cell cultures to produce vaccines used for humans. Porcine skin has been used to repair burns on human bodies. Pigs have also contributed insulin and heart valves to save human lives. There may be little to no difference between xenotransplantation and the use of these biological materials that have not been sterilized (Murphy 1996).

At a conference held in July of 1996 the Institute of Medicine of the United States and the Nuffield Council on Bioethics of the United Kingdom both came to the same conclusion of supporting the future research and trials of xenotransplantation. They each made strong arguments that the probable benefits that could be gained from this type of transplantation outweighs the possible risks that are involved (Marwick 1996). The Nuffield Council reported that "it would be unacceptably conservative to prohibit an innovation on the grounds of transmitting possible viruses." The Institute of Medicine stated that "as members of society we can't run away from the risks that may be involved in helping those in need." With the thousands in need and the shortage of human donors, something needs to be done and xenotransplantation may be the best option.

Even though the Institute of Medicine has given the go ahead to further proceed in the direction of animal-to-human transplant, caution was of major concern. The issues of importance included regulations on animals and procedures being used as well as specific guidelines to inform patients, the public, and other professional involved. In August of 1996 the American Society of Transplant Physicians issued the guidelines set forth by the Public Health Service that are to be followed in the case of transplanting animal organs or
tissue into humans. The Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantations focuses on four specific concerns. These concerns include the clinical issues, animal issues, recipient issues, and record keeping issues. The role of this draft is to help reduce public health risks that are connected with xenotransplantation without limiting the availability of promising treatments for those with a life-threatening illness.

The clinical plan is the first section of these guidelines. It involves several regulations that are to be followed concerning the clinical center. The professional team participating in the xenotransplant should include a surgeon, an infectious disease physician, a veterinarian, a transplant immunologist, an infection control specialist, and a clinical microbiologist. The facility should have an accredited microbiology and virology laboratories. The center should have a Biosafety Committee that reviews each protocol which will also be looked over by the Institutional Animal Care and Use Committee, the Institutional Review Board and FDA. This protocol should clearly state the types of screening methods that will be used as well as revealing the potential risks to the patient and those in close contact of the patient.

The concern of the animals and their sources are addressed in the second section. The donors animals should be taken only from well screened and closed herds. These colonies must be carefully characterized and protected against as many potential agents that may cause infections as possible which means that all animals are to be bred and raised in captivity. There should also be accurate and specific records made of the lineage all animals.
The issues surrounding the recipient and clinical staff are also important. Several of the highlights of these regulations are as follows. The condition of the patient's health is to be monitored not only clinically but also through specific tests run in the laboratory. These lab tests must be determined and carefully recorded before the transplant takes place. The recipients of these animal donors must be informed of the possible risks to themselves as well to close contacts. These close contacts should also be educated of the risks involved as well as the health care team participating in the monitoring of the recipient. Laboratories of the facility must be available to culture and identify agents that could cause infection. Samples of each patient's serum is to be collected and stored for future reference. Careful records must be maintained and must be done in a manner that protects the confidentiality of every patient.

The final section of the guidelines address public health needs. A proposal is made for a national registry. This would aid in the identification of health problems that are concerns of the public that are associated with xenotransplantation. Communication is the key factor in these regulations set up by Public Health Service. The FDA is to play a role in the design of this registry. They are also responsible for providing the framework of the regulations on these new biological experiments. The protocols for each xenotransplant must follow the guidelines of the Investigational New Drug application and must be filed with the FDA for approval.

Although xenotransplantation has not been completely mastered by scientists today, it is advancing quickly and shows a promising future in saving tens of thousands and maybe even millions of lives. There are many unknown factors that are playing a
critical role in the concerns of people nation wide. The past three years have shown a
tremendous leap in knowledge and a large number on the unknowns are becoming known.
Science cannot be afraid of the risks involved in this opportunity but they should be
cautious of the risks involved, careful with their strategies, and open in communication
with others so that everyone can be well informed of the progress and the risks. In the
words of Thomas Starzl, "science has progressed far enough that real lives hang in the
balance, not to pursue further progress would clearly be unjustifiable" (Hanson 1995).
Works Cited


From Chimeric Donors In A Mouse To Rat Xenotransplant Model. Transplant Proceedings, Vol. 28, No. 2, 733-734.


Works Consulted


