

**Highlights of the First Meeting of the  
Secretary's Advisory Committee on Xenotransplantation  
February 20-21, 2001  
DoubleTree Hotel, Rockville, MD**

**Background**

The Secretary's Advisory Committee on Xenotransplantation (SACX) was chartered to advise the Secretary, Department of Health and Human Services (DHHS), on all aspects of the scientific development and clinical application of xenotransplantation. This includes the full range of complex scientific, medical, public health, ethical, legal and socioeconomic issues related to xenotransplantation.

The Committee's charge includes advising DHHS on the current state of knowledge regarding xenotransplantation; reviewing current and proposed xenotransplantation clinical trials and identifying and discussing important issues raised by the research; advising on the potential for transmission of infectious diseases as a consequence of xenotransplantation; recommending, as needed, changes to the *PHS Guideline on Infectious Disease Issues in Xenotransplantation*; and to discuss and address additional issues and international developments that are relevant to xenotransplantation. The recommendations of the Committee will facilitate DHHS efforts to develop an integrated approach to addressing emerging public health issues in xenotransplantation.

The SACX convened for its first meeting on February 20-21, 2001. The meeting was primarily for orientation and organizational purposes. The first day began with the swearing in of committee members and opening remarks by Dr. David Satcher, Surgeon General of the United States, followed by an overview of the Federal Advisory Committee Act and the ethics rules for advisory committee members. This was followed by presentations on the experimental and clinical history of xenotransplantation and on the current state of the science of xenotransplantation. The afternoon began with presentations on the recently issued *PHS Guideline on Infectious Disease Issues in Xenotransplantation* and FDA regulation of xenotransplantation, followed by the first of three presentations on xenotransplantation clinical trials.

The second day began with two additional presentations on xenotransplantation clinical trials, followed by presentations and discussion to identify the range of issues raised by xenotransplantation in the areas of science, public health, ethics, animal welfare, socioeconomics, law, and psychology, along with presentations from the perspective of patients and of Federal agencies. Time was set aside for public comment on both days.

## Opening Remarks

Dr. William Raub, Deputy Assistant Secretary for Science Policy, noted that DHHS has been working on the topic of xenotransplantation since 1994, when the shortage of human organs for transplants led to increased interest in the clinical use of animal organs and tissues. DHHS formed several interagency working groups to explore the public health risks raised by xenotransplantation and to reach consensus on baseline safety standards for the procurement, screening, and use of animal tissues and for clinical follow-up of human recipients. Workshops and public meetings in 1995 and 1996 led to the publication of the draft *PHS Guideline on Infectious Disease Issues in Xenotransplantation* in the Fall of 1996. Since then, an interagency working group has been working to develop and refine DHHS strategy in five areas: (1) an evolving regulatory framework for xenotransplantation clinical research, (2) a revised version of the draft *PHS Guideline*, (3) a national database of xenotransplantation clinical trial information, (4) an archive of biological specimens from xenotransplantation patients and source animals, and (5) a national advisory body and public forum on issues involving xenotransplantation. DHHS components involved in this strategy have been the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and Health Resources and Services Administration (HRSA), with oversight and leadership by the Office of the Secretary (Office of the Assistant Secretary for Planning and Evaluation and Office of the General Counsel).

Dr. David Satcher, Surgeon General of the United States, administered the oath of office to the members of SACX. In his remarks, he explained that the demand for transplanted human tissues and organs has outstripped the supply of human materials. At present there are 75,000 Americans on waiting lists but only 22,000 transplants take place each year, and in 1999 alone 6,100 Americans died while waiting for a human organ transplant. Recent advances in immunology, molecular genetics, and bioengineering have overcome some of the short-term scientific and clinical barriers in transplanting animal organs and tissues into humans, but attention is still needed in the long-term implications of xenotransplantation, including delayed immune rejection, public health risks, law, and ethics. The public health challenge is to balance the promise of this technology with the risk of infection by known and novel pathogens. The SACX is charged with advising the Secretary on all of the complex issues raised by xenotransplantation and to make recommendations on DHHS policy and procedures.

Dr. Harold Vanderpool, Chair of the SACX, asked the members to introduce themselves and to describe the expertise they bring to the Committee. He added that the breadth of the committee reflects the broad range of issues they had been asked to address. He promised to involve all members, remain open to all views, and to be receptive to public comments. The central task for this meeting is to gain a quick background in the science of xenotransplantation and to identify and possibly prioritize the issues that the committee will need to address.

Dr. Mary Groesch, Executive Director of SACX, explained that Committee members are “special government employees” during their participation in SACX meetings. Ms. LaVerne Stringfield,

Office of Federal Advisory Committee Policy, NIH, described the roles and duties of members under the Federal Advisory Committee Act of 1972, including reporting and accountability. Karen Dalheim, Office of the General Counsel, DHHS, described the ethical guidelines for advisory committee members, including conflicts of interest and confidentiality. In response to questions, she explained that members can give personal opinions to the news media but should not speak for the committee without prior clearance from the Executive Director/DHHS. In addition, members cannot engage in lobbying activities while a Committee meeting is in session. Committee members also may not profit personally from information gained during those meetings, nor accept honoraria and other remunerations from foreign governments. She advised members to ask first, if there was a question, or to refer to the NIH ethics website at <http://ethics.od.nih.gov>.

### **Experimental and Clinical History of Xenotransplantation**

Dr. David Cooper, Harvard Medical School, reported that physicians transfused blood from animals to humans as far back as the 18th century, and the 19th century included some efforts in xenotransplantation skin grafts, especially from frogs to humans. He noted that Serge Voronoff attempted to “rejuvenate” aging male patients in the 1920s by transplanting tissue from the testicles of chimpanzees and baboons, and by the 1960s there had been numerous kidney, heart and liver transplants, usually from nonhuman primates, with survival times ranging from hours to months. More recently, physicians infused baboon bone marrow cells into an AIDS patient, and in uncontrolled studies patients have received “rejuvenating” infusions of sheep fetal cells at Clinique la Prairie in Switzerland.

In the past 15 years, attention has shifted from primates to pigs as xenotransplantation source animals, for medical, public health, and logistical reasons. Porcine organs and vascularized tissues are subject to a rapid and dramatic rejection by the immune system of the human recipient. This hyperacute rejection is caused by antibody-mediated complement activation in response to certain galactose residues ( $\alpha$ Gal), an antigen that is found not only on the surface of porcine blood vessels, but also on the surface of many bacteria and viruses and on the cells of all mammals except humans and old world primates. Humans develop antibody to the  $\alpha$ Gal on the surface of bacteria that colonize the bowel, and these antibodies cross-react with the  $\alpha$ Gal on the porcine vessels, triggering activation of complement and a vigorous rejection of the porcine organ within minutes. It is possible to remove the anti- $\alpha$ Gal antibody from the patient’s blood prior to the xenotransplantation procedure, but it returns in about a week and cannot be suppressed permanently. This led researchers to develop a transgenic pig whose tissues express human complement regulatory proteins that will protect the transplanted organ against the complement activation caused by the recipient’s anti- $\alpha$ Gal antibodies. This has led to survivals of a couple of weeks for the heart and months for the kidney, in animal models.

Progress in xenotransplantation techniques has led to concerns with other issues, including the risk of infection and the functional success of the transplanted organ. It has also raised a number of associated issues, including the ethics, regulation, legal aspects, and costs of

xenotransplantation. The speaker predicted that, in the long run, xenotransplantation will succeed and will ultimately receive public acceptance because, in the words of Sir Peter Medawar, “people are so constituted that they would rather be alive than be dead.”

## **Science of Xenotransplantation**

### *Immunological Aspects*

Dr. Hugh Auchincloss, Harvard Medical School, reminded the audience that there are potential alternatives to allotransplantation and xenotransplantation that are being or have been actively pursued by researchers, including artificial lungs, an implantable heart, a left ventricular assist device, implantable kidney dialysis devices, and non-invasive glucose monitoring coupled with an insulin pump system. However, xenotransplantation is already taking place, and a growing scientific literature indicates that survival times are increasing steadily. This raises four issues about the clinical efficacy of xenotransplantation.

The first set of questions has to do with the physiological function of a transplanted organ. Will/does the animal tissue or organ survive and function adequately to support human life? While the organ may survive for several months, it does not always function perfectly in the human recipient. For example, baboon livers do not metabolize uric acid in the same way a human liver does, resulting in low serum levels of uric acid and cholesterol. Similarly, the erythropoietin produced by a pig liver does not stimulate the production of red blood cells in the human recipient, resulting in severe anemia. The latter problem might be solved by developing a transgenic pig that expresses human erythropoietin. In general, however, the more complex the organ, the more likely that its physiological function will not support human life.

A second, immunological problem in xenotransplantation is the natural or preformed (anti- $\alpha$ Gal) antibodies present in humans that can destroy organs from many non-human animals, including pigs. Humans have natural antibodies against the galactose-containing antigen that is expressed on the endothelial cells of vascularized organs from pigs and all other mammals except humans and old world monkeys. (This problem doesn't arise with cellular transplants, which involve no vascular endothelium and hence no  $\alpha$ Gal.) The binding of human anti- $\alpha$ Gal antibodies to the galactose-containing antigen on the surface of endothelial cells leads to complement activation and then to activation of the endothelium. Endothelial activation results in interstitial hemorrhage and intravascular thrombosis, the two main features of hyperacute rejection, within minutes to hours.

Within a given organism, there are complement regulatory proteins that control the activation of the complement cascade. However, complement regulatory proteins often don't work across species, and such is the case with pigs and humans: porcine complement regulatory proteins are incapable of downregulating the activation of complement when the complement comes from the human recipient. Molecular approaches to overcoming these problems have been (1) to prevent the expression of galactose and/or (2) to augment the function of human complement regulatory

proteins. Over the past ten years, the development of transgenic pigs that can regulate hyperacute rejection or avoid its onset have been surprisingly successful. This has involved engineering pigs with human complement regulatory proteins.

A third problem is delayed xenograft rejection or acute vascular rejection, which thought to be an antibody-mediated process. The type of endothelial activation that occurs in delayed xenograft rejection leads to a procoagulant environment and, eventually, vascular thrombosis. Because the molecular causes of this physiological dysregulation are less well understood, delayed xenograft rejection is the scientific obstacle to xenotransplantation that is the block to progress in the field at this time. In an effort to avoid the delayed xenograft rejection by a pharmacological means, investigators have turned to a variety of immunosuppressant agents that are largely directed at B cell suppression, coupled with transgenic animals that avoid hyperacute rejection, but at present the survival of porcine vascularized organs in a nonhuman primate recipient is no more than two months. Is this sufficient to justify clinical trials in humans?

The fourth immunological problem is cell-mediated xenograft rejection, a longer term response that has not yet become a practical issue. CD4 T-cells appear to be important in this process, and even though cell-mediated rejection occurs through an indirect pathway (i.e., using the antigen-presenting cells of the recipient rather than those of the source animal), this type of rejection is much stronger in xenograft rejection than in allograft rejection. The reasons for this are unclear, although it may involve the activation of natural killer cells in response to pig antigens. General approaches to all of these immunological problems are to reduce the number of foreign antigens and to restore an orderly physiological regulation.

In response to questions, Dr. Auchincloss added that there is no evidence that human recipients would tolerate porcine transplants better than do nonhuman primates. However, we can take better care of human patients than non-human primates, because we have a greater ability to monitor and control human physiologic functions through life support devices and drugs, and so we might anticipate a better outcome in human trials. An FDA advisory subcommittee and an international society have discussed, as a threshold for moving from animal to human trials, 90-percent survival for two months and 50- or 60-percent survival for three months. Some participants think this is an unreasonably high standard, given the differences among primates. Auchincloss feels that a more meaningful standard would be a new understanding of, and solution for, the problem of delayed xenograft rejection; this is a problem that requires a better scientific understanding of the rejection processes.

### ***Preclinical Animal Models***

Dr. David White, University of Western Ontario, suggested that the ability to change the source species through genetic engineering (techniques such as nuclear transfer and homologous recombination) provides a major opportunity for the future of xenotransplantation and for therapeutic medicine in general. Using genetic engineering techniques, researchers have inserted

into the pig genome the genes for a number of human complement regulatory proteins and have also succeeded in cloning techniques for pigs.

The central questions at present have to do with the “comfort factor” — what results from preclinical research justify the initiation of human trials with whole organ xenotransplantation? Is pig-to-primate a valid model for humans, what level of success should be required in animal trials, and how long must xenografts survive in nonhuman primates before they are attempted in humans, and how long should nonhuman organs be expected to survive in humans? Current data for pig-to-primate transplants are 38 days for heart and 78 days for kidney, but current immunosuppressive strategies clearly begin to fail at about 40 days.

There are a number of reasons why xenotransplantation might fail in nonhuman primates yet succeed in humans, notably the wide biological and microbiological differences between human and nonhuman primates and even among nonhuman primates. Most immunosuppressive and antibiotic drugs have been developed for humans, not animals, as have the reagents and procedures used in these experiments. In addition, the transgenes used in the pig source animals are human, and the primate recipient may develop antibodies against that human transgene, rather than against the pig organ itself. This type of immune response may limit the usefulness of the nonhuman primate model. (Human transgenes are used because the ultimate goal is xenotransplantation to humans.)

In conclusion, White suggested that the pig-to-primate model is essential for proof of concept studies, but may be of little value in defining the details of immunosuppressive regimens. The nonhuman primate is a difficult model for testing this, but as yet we have nothing better. The question is whether this model is valid for humans. To resolve this question, it may be necessary to compare the results of animal and human clinical trials, once the procedure has been tried in humans. White also concluded that the pig is a suitable source of organs and cells genetically engineered for man.

### ***Infectious Disease Risk***

Dr. John Coffin, Tufts University, addressed the risks of viral infections from xenotransplantation, stating that with respect to bacteria and parasites, the issues are not much different than they are for other kinds of transplantation. There are two levels of infectious disease risk that we are concerned about. There is a risk to the recipient which, given reasonable control measures, is likely less for a xenotransplant recipient than it is for an allotransplant recipient. The main concern is the potential risk to the public. That is, there is a remote possibility that a new infectious agent or a novel transmission mode will be inadvertently created by the intense co-cultivation of the transplant cells with the cells of the recipient. Examples from recent history point to the seriousness of this risk: canine parvovirus (cats to dogs); Ebola virus (source unknown); HIV (chimpanzee to human); and subgroup J avian leukosis virus (chicken to human). There are dozens of known disease agents in pigs, many others that are capable of infecting human cells in vitro, and a number that belong to families that are known to change

hosts or virulence. Control measures include breeding, screening and monitoring of donor animals, but serious challenges remain.

Retroviruses pose a special threat because they are incorporated into the host's DNA, and indeed provirus DNA (a combination of host and retroviral DNA) comprises a significant fraction of the genome in all species, and humans may have more proviruses than genes. In humans, most of these "fossil" proviruses are old and defective, but some proviruses from pigs (and other animals) can yield infectious viruses. Notable examples are the gamma retroviruses, which cause murine and feline leukemia and other diseases. In particular, porcine endogenous retrovirus (PERV) is present as more than 20 proviruses in all known breeds of pigs, and at least 6 of these can infect human cells. These viruses are expressed at low levels but do not cause disease in pigs. Because they are present in all pigs, they are hard to remove by selective breeding, although it may be possible to develop a knockout pig once the PERV sequences are known.

The risk of transmitting infectious agents during xenotransplantation is currently unquantified. The risk to the recipient is probably as acceptable, certainly in life-threatening situations, as it is in allotransplantation. Of much greater concern is the remote possibility also of generating a virus that could be transmitted from one individual to another. Dr. Coffin suggested that this risk may well vary with the nature of the transplant (e.g., a relatively small number of cells vs. whole organs), the extent of chimerism being created, the amount of time the animal and human cells are in contact, and the extent of immunosuppression.

The risk is likely to be reduced by natural immunity, because the preformed antibodies against  $\alpha$ Gal are likely to be strongly neutralizing for viruses. However, once the virus replicates within a human cell, it acquires human surface molecules and no longer expresses  $\alpha$ Gal. Evidence from animal studies suggests that when porcine viruses are injected into guinea pigs or immunodeficient mice, they spread transiently and then are eventually suppressed by an induction of immune response. In addition, there was no evidence of an ongoing fulminant infection in the animals or any pathogenic consequences. In addition, a study was published examining 160 human patients exposed to porcine cells, and no evidence of infection could be found.

Important measures to minimize the risk of infection and subsequent human-to-human transmission of disease include monitoring recipients for evidence of infection or associated disease, minimizing their ability to transmit disease (e.g., deferment from blood donation), education about transmission,. Other, more theoretical measures include prophylactic treatment for infection, removing active proviruses from animal sources by selective breeding or knockout, developing transgenic pigs that suppressing PERV expression, and monitoring of contacts.

A number of factors should be considered in estimating risk. First, viruses like PERV do not infect adult animals very well, and are generally transmitted vertically to immuno-incompetent offspring (there are exceptions of course). Second, endogenous viruses replicate poorly and have low pathogenicity in general, although certain mutations or recombination with endogenous

proviruses can restore pathogenicity and replication competency. At present, however, there is no evidence of human infection with such porcine endogenous viruses, and certainly no evidence of disease, despite millennia of close pig-to-human contact. However, xenotransplantation is a novel kind of close contact, and the extent to which it can promote the different ways of introducing infectious agents remains to be seen. So far, there is no evidence for infection following xenotransplantation with the hundreds of patients that have been examined, but the question remains if we are looking in the right place.

In response to questions, Dr. Coffin added that most human proviruses are about 5 million years old, while some porcine proviruses are far more recent. We have not yet studied the disease potential of our own proviruses, but there seems to be little potential for creating a new disease organism by transfecting human genes into donor animals. The chair indicated that SACX would want to spend more time on this topic in the future and would invite Coffin back for further discussion and updates.

### **Public Comment**

Dr. David Cooper, speaking on behalf of the International Society for Heart and Lung Transplantation, reported that this organization has developed conclusions and recommendations about the role of xenotransplantation. The Society also developed guidelines for the level of success in pig-to-primate animal models that should precede human clinical trials of whole organ xenotransplantation. Namely, ten animals which formed at least 60 percent of a group of animals, all having the same treatment, where the pig organ supported the life of the baboon for at least three months, with some of the animals surviving to six months, and without a high degree of debilitation. Their consensus was that with the current state of the science, we are not ready for clinical trials in humans in which whole animal organs are transplanted, and that it will be necessary to resolve the risk of infection to the public. Pediatric specialists want to include infants and children, and there is evidence that, with their undeveloped immune systems, children might have better results than adults.

Dr. Leonard Bailey, Loma Linda, spoke briefly about his experience with transplanting a baboon heart into Baby Fae (1984) and stated his opinion that infants should be considered for participation in xenotransplantation clinical research, as they may provide a window of opportunity that does not exist with adults. He also mentioned that there are archived specimens from Baby Fae that could be studied for evidence of transmission of infectious agents. He also urged the Committee to keep an open mind about the appropriateness of the baboon as a source animal, particularly for AIDS-related uses.

Dr. Mrunal Chapekar, National Institute of Standards and Technology (NIST), reported that NIST's Advanced Technology Program sponsors private companies to conduct high risk research, including xenotransplantation at the basic and animal levels. NIST-sponsored xenotransplantation follows current guidelines and will adhere to any future changes in those guidelines.

Dr. Hugh Auchincloss raised questions about the status of the FDA xenotransplantation subcommittee and international regulation of xenotransplantation. Dr. Jay Siegel (FDA) noted that the FDA subcommittee has a different charter and role from SACX, and there has been no decision on whether the subcommittee will continue. Regarding the international issues, it was pointed out that the Public Health Service held an international workshop in 1998, and the PHS draft guidelines would provide guidance for many other nations. Nevertheless, there is a real danger of “rogue” xenotransplantation programs, and it will be important to advise the Secretary on the need to deal with international issues. There was general agreement by committee members that the issue of international cooperation and possibly regulation regarding xenotransplantation is critically important. The Chair indicated that the committee would address this issue on day two, and it was suggested that future meetings might include observers or presentations by foreign governments and international bodies.

Ms. Maria Tallacchini, Kennedy School of Government at Harvard, noted that the concepts of informed consent and individual autonomy and responsibility may be somewhat at odds with the public health requirements and constraints that may accompany xenotransplantation, and that it may be difficult to enforce compliance with safety measures.

Dr. John McArdle, Alternatives Research and Development Foundation, suggested that it would be useful to have information on funding levels for basic and clinical xenotransplantation research, research on alternatives to xenotransplantation, and efforts to improve organ donation. He voiced a concern that if xenotransplantation goes into clinical practice, we may need to consider whether the source animals need special care standards that are not covered by current regulation or law, such as measures to minimize behavioral and environmental deprivation. He also encouraged the Committee to keep abreast of alternatives to xenotransplantation, including efforts to increase human organ donation.

## **Regulation of Xenotransplantation**

### ***PHS Guideline on Infectious Disease Issues in Xenotransplantation***

Dr. Louisa Chapman, CDC, reported that the draft *Guideline* was originally published in September 1996, and that the revised *Guideline* released in January 2001 is available online at <http://www.fda.gov/cber/gdlns/xenophs0101.htm>. It provides guidance to researchers and sponsors on how to prevent or minimize the risk of infection associated with xenotransplantation, and how to control infections if they occur. There are five areas of emphasis: (1) protocol development and review; (2) the informed consent and education processes; (3) pre-xenotransplantation screening and post-xenotransplantation monitoring to reduce the risk of infection; (4) hospital infection control practices, including BSL-3 for unknown agents; and (5) archiving specimens and information for 50 years on donor, recipient and contacts.

In response to questions, Dr. Chapman added that there are few precedents for the lifelong surveillance and required autopsy that are called for in the *Guideline*. However, there are

examples of infectious agents with latency period of 10 to 60 years and OSHA requirements for maintenance of records for 30 years. This is an evolving document that may be revised in the future, in response to more extensive experience with xenotransplantation. Committee members noted that in some cases the responsibility for maintaining archives would outlive the companies that supply animals, the careers of surgeons and nurses, and even the hospitals in which transplants take place. For this reason, the revised *Guideline* calls for the creation of a publicly funded archive, which is currently in the planning stage. The document contains very little by way of addressing noncompliance, and current standards hold the autonomy of the individual paramount, but officials can invoke quarantine if there is a documented imminent threat to the public health.

### ***FDA Regulation of Xenotransplantation and Current Policy***

Dr. Eda Bloom, Center for Biologics Evaluation and Research (CBER), FDA, defined xenotransplantation as any procedure that involves the transplantation, implantation, or infusion into a human recipient of either a) live cells, tissues, or organs from a nonhuman animal source, or b) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

Dr. Bloom described the history and current status of FDA regulatory actions relevant to xenotransplantation. In 1993, FDA published a document on cell and gene therapy products that, for the first time, set forth that the use of xenogeneic cells was regulatable by FDA. The first Investigational New Drug (IND) application for a xenotransplantation product was received in 1994, raising unique safety concerns. This led to a number of cooperative efforts among PHS Agencies and publication of the draft *PHS Guideline on Infectious Disease Issues in Xenotransplantation* in 1996. In 1997, when it was shown that PERV could infect human cells, FDA placed all clinical trials using porcine xenotransplantation products on hold until researchers could demonstrate the ability to test for PERV. FDA created a Xenotransplantation Action Plan in 1998, making xenotransplantation a focus of the Agency. Since that time, additional guidance documents on public health issues, safety precautions, source animals, and a proposed rule on public disclosure in regard to xenotransplantation have been issued as part of the Agency's goal of developing a cohesive policy on xenotransplantation.

For reviewing xenotransplantation INDs and developing guidance, FDA has formed large teams to address the complex issues and data resulting from xenotransplantation research, including an IND reviewer focus group and a xenotransplantation subcommittee of the Biological Response Modifiers Advisory Committee. CBER also conducts xenotransplantation-related research in order to aid in policy development. FDA also collaborates with other agencies, for example on the revision of the draft *Guideline* and in the ongoing development of a national xenotransplantation archive and database. Further information on FDA activities and documents can be obtained at <http://www.fda.gov/cber/xap/xap.htm>.

Dr. Bloom described recent recommendations of FDA advisory committees and highlighted three particular FDA guidance documents and one proposed rule in the area of xenotransplantation: Guidance for Industry: Precautionary Issues Posed by the Use of Non-human Primate Xenograft in Humans; Draft Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Close Contacts; Draft Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans; and Proposed Rule: Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation.

In response to questions, Dr. Bloom added that FDA guidances are very responsive to public comment and often go through several review cycles. The Agency tries to provide flexibility to manufacturers in how they meet safety goals, so long as they can demonstrate that alternative approaches meet the same standards. FDA is also very concerned about protecting both trade secrets and “patient-identifiable” information in the design of the xenotransplantation database.

## **Presentations on Xenotransplantation Clinical Trials**

### ***Overview of Xenotransplantation Clinical Trials***

Dr. Louis Marzella, FDA, described the stages of clinical research on new drugs and procedures. Phase 1 trials, tending to be small (20 to 50 participants), are the first introduction of a product into humans, and are designed to assess the safety of the product. Phase 2 trials might involve up to 100 subjects, and while they continue to assess safety, they also begin to collect information on the biological activity of the product. Phase 3 trials are larger (100-1000's subjects) and are often multicenter efforts seeking to establish the clinical benefit of a product and determine the risk-benefit. Post-marketing studies involve the ongoing collection of safety data. FDA can place a trial on clinical hold at any stage in this process if it determines that there are significant and unreasonable risks, inadequate safety information, an unqualified investigator, or (at Phase 3) an inadequate study design.

At present there are four major classes of xenotransplantation products: solid organs used *ex vivo*, cell implants, artificial biologic organs, and autologous or allogeneic cells which have had either *in vivo* or *ex vivo* contact with nonhuman cells. There are currently no INDs filed for whole organ xenotransplantation *in vivo*, although there has been extensive pre-IND discussions about proof of concept studies in this area. Examples of xenogenic cell implants include porcine fetal neuronal cells for treating Parkinson's and Huntington's disease, porcine hepatocytes for treating acute or chronic liver failure, and the use of bovine adrenal chromaffin cells for managing intractable pain in cancer patients. Examples of use of whole organs or artificial biologic organs include extracorporeal perfusion of human blood through whole porcine liver and plasma perfusion through hollow fiber devices containing porcine hepatocytes for patients with acute liver failure. An example of human tissues that come into contact with nonhuman

cells is lymphocytes (active against specific leukemic cells) expanded in SCID mice for the purpose of immunotherapy for metastatic cancer. These products are in a range of clinical stages of development, from pre-clinical to advanced trial stages.

### ***Excorp Medical Bioartificial Liver System***

Dr. Daniel Miller, Excorp Medical Inc., noted that his company has benefitted from an evolving and maturing relationship with FDA in the development of their Bioartificial Liver System. This product, which is designed to serve as a bridge to organ allotransplant or as a means for permitting liver regeneration, circulates the patient's blood through a bioreactor containing porcine hepatocytes that replace the metabolic functions of the patient's liver. The reactor membrane has a molecular weight cutoff of 100 kilodaltons, small enough to prevent the passage of viruses and antibodies and large enough to allow the passage of the intended molecules. Dr. Miller stated that this technology had shown promise in animal models of liver failure, and Phase I/II clinical trials began in November 1998 at the University of Pittsburgh. These trials have demonstrated the safety and some clinical benefit of the system, transiently reducing levels of waste products and improving pulmonary efficiency. He further said that the manufacturer has adhered to FDA guidelines in the biosafety measures, including monitoring the source herd for xenozoonotics.

In response to questions, Dr. Miller explained that boars are bred separately and sows are fertilized by artificial insemination. Specimens are being archived but researchers are not yet testing for antibodies to  $\alpha$ Gal or hepatic factors. Most recipients are not immunosuppressed. Researchers are developing new assays for PERV and other porcine viruses, but they are confident that the screening membrane is sufficiently tight — it might pass subunit proteins and viral fragments, but no intact molecules. The technology will require public awareness and confidence to succeed, and he hopes that FDA will continue to provide enough flexibility to permit development and commercialization.

### ***Drosophila Cell Stimulated Autologous CD8 Lymphocytes for the Treatment of Advanced Melanoma***

The research described by Dr. Jon Richards, Oncology Specialists S.C., was an example of “part b” of the PHS and FDA definition of xenotransplantation, that is, the transplantation, implantation, or infusion into a human recipient of human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs. Dr. Richards described a clinical protocol for treating advanced melanoma that exploits the ability of stimulated immune cells, known as cytotoxic T lymphocytes (CTLs) to search out and selectively kill specific cells. In this case, the target cells are melanoma tumor cells, and the stimulator cell is a *Drosophila* cell that has been transfected with a variety of human genes, including for some melanoma tumor-associated proteins. The cycle of isolation, stimulation, expansion, and reinfusion takes about six weeks and results in a fourfold expansion of activated CTLs, at least in a mouse model. Dr. Richards believes that CTLs are an ideal therapeutic vehicle because they

are highly specific, nontoxic, and effective against metastatic and recurrent tumors. Melanoma is the initial disease target because its antigens are well characterized and the lesions are easy to see and measure.

In response to questions, Dr. Richards added that 13 of 14 patients were previously treated with interferon to increase the expression of markers on tumor cells, and that lesions shrank in response to therapy. Twelve of the 14 patients had since died — median survival with melanoma is only 2.5 years. The transgenic *Drosophila* cell line is now eight years old, and a new working line is created every three months. Human cells are in contact with *Drosophila* cells for seven to nine days, and no *Drosophila* DNA has been detected in the activated cells. Tumor load was not considered in determining dosage.

### ***XenoCell Transplantation in Human Clinical Trials***

Dr. Michael Egan, of Diacrin Inc., reported that his company has a number of cellular therapy products currently in development. Their collaborator in developing treatments for Parkinson's and Huntington's disease is Genzyme LLC. Parkinson's disease is a progressive neurodegenerative disease characterized by the loss of dopamine production. As the disease progresses, drug therapy is less and less effective. Diacrin's approach involves the implantation of fetal pig neuronal cells into the brain by stereotactic surgery, in conjunction with immunosuppression.

Diacrin applied for IND status in July 1994 and enrolled its first patient in April 1995, but the trial was placed on clinical hold in 1997 due to concerns about PERV. That hold was lifted in December 1999, and the company now foresees BLA approval in the first quarter of 2004. They have received considerable regulatory guidance and oversight, and they are also in contact with regulatory agencies in Canada and the United Kingdom.

Phase 1 involved 12 patients, one of whom has died, and photomicrographs on autopsy showed that the implanted pig cells were sending out processes, suggesting survival and permanence. No sign of PERV infection has been observed by Diacrin after five years. Phase 2 involves 18 subjects, approximately half of whom are controls, and this trial will be unblinded soon. Phase 3 will involve 36 patients, half of them controls.

Dr. Egan stated that Diacrin is a participant in the pilot study of the PHS national xenotransplantation database and has in place a comprehensive surveillance regimen for herd animals, patients, and contacts. The informed consent process includes education and training on issues such as the need for extended surveillance, for refraining from blood and tissue donation, for using condoms, and for educating close contacts. Dr. Egan further stated that the Diacrin informed consent document is approximately 40 pages long.

Dr. Egan showed a short film clip of the first patient who received a porcine cell implant. There was a dramatic difference in mobility and motor control before and after the implant, and Egan noted that this response has been seen in a number of patients.

In response to questions, Dr. Egan said that the company had introduced screening for additional infectious agents, including hepatitis B and circovirus, and that animals in the two source herds tend to be in very good health. Contaminants have not been a problem. He also noted that the consent form is pretested for comprehensibility, and subjects receive neuropsychiatric evaluation and educational refreshers on a regular basis. Subjects tend to be late-stage Parkinson patients, and typical results are a 30-percent improvement in UPDRS scores (an imperfect measure). Typical dosage is 48 million cells, with controls receiving a sham operation in Phase 2; this will not be repeated in Phase 3.

### **Identification of Issues in Xenotransplantation**

Committee members chosen by the chair gave short presentations on issues of potential concern, followed by discussion and questions from the committee as a whole. The purposes of this session was to identify the range of issues raised by xenotransplantation that could be addressed by the SACX, and to begin the process of prioritizing among them and identifying possible topics for future meetings of SACX. The committee identified issues in the following areas:

#### ***Scientific and Medical Issues***

- Medical risks and benefits of xenotransplantation. This should be addressed both as a function of the disease (i.e., is it an acute lifesaving measure vs. treatment of a chronic disease) and as a function of the treatment strategy (i.e., temporary bridging vs. long-term implant; vascularized organ vs. nonvascularized cells, possibly encapsulated).
- Immune rejection. There has been considerable success in overcoming hyperacute rejection, but much remains to be learned about the causes and cures for acute humoral and cellular rejection and chronic rejection.
- Validity of animal models. Are animal models reliable predictors for determining whether/when it is time to move forward with human clinical trials? Current standards may be unreasonably high, particularly in view of the variability among nonhuman primates. There is a need for validation of results from rodent and primate trials. Experience in HIV research points to the same problem.
- Immunosuppression. How much immunosuppression is enough, or too much? The success of human-to-human transplantation has come with higher and higher levels of immunosuppression, but this may not be appropriate for xenotransplantation. Allograft immunosuppressive drugs need to be validated for use in xenotransplantation. Topics of

particular concern include the inhibition of complement, natural antibodies, clotting cascade, monocytes, and cytokines.

- Tolerance. What strategies can improve the long-term tolerance of xenotransplantation organs and tissues? Both natural antibodies and xeno-specific antibodies are of interest.
- Cell biology/physiology of xenotransplantation. The survival of the patient is a different matter from the survival of the transplanted organ or tissues, which in many cases may not produce the same hormones, growth factors etc. as the human organ/tissue it replaces or supplements. What proteins are secreted by the transplanted organ, can they be regulated, and how does the host's immune system respond to them? A "Porcine Genome Project" might be needed to answer these questions. Related questions concern extracellular adhesion and the ability of the transplanted organ to repair injury.
- Long-term effects of genetic engineering. What are the broader, downstream, and cumulative effects of genetic engineering? Little is known about the long-term impacts of overexpressing a transfected gene, especially from another species.
- Porcine Endogenous Retrovirus (PERV). What effect does the process of xenotransplantation have on PERV proviral transcription? Aside from the public health issues (below), what is known about PERV activation, expression, receptors, target cells? What effect does genetically engineering (e.g., removing  $\alpha$ Gal residues or inducing tolerance to  $\alpha$ Gal) have on PERV, and can PERV be a contributing factor in acute or chronic rejection? What effect will long-term immunosuppression have on PERV?
- Alternatives to xenotransplantation. There are or will be alternatives to xenotransplantation, and the committee should keep abreast of such alternatives such as stem cells, gene therapy, artificial organs, etc. and should re-evaluate the risks and benefits of xenotransplantation in light of progress in these different areas.
- Pre-clinical research. Who will fund and conduct the research needed to answer the critical unanswered scientific questions identified here and elsewhere? Industry can't be expected to do this long-term, basic research. Will adequate funding be available? Do we have adequate scientific manpower to pursue these questions?

### ***Safety and Public Health Issues***

- Risk of infection. How can we determine/quantify the risk of transmission of an infectious agent due to xenotransplantation? Is the chain of infectious transmission possible? That is, can the animal microbe be transmitted to a human, can it survive and replicate, will it cause disease, and can that disease be transmitted to others? Transmission can't be assumed, and if the microbe doesn't cause disease, or if that disease isn't infectious, then it may be of relatively little consequence.

How can we minimize the risk of infection from xenotransplantation? It may not be possible to achieve a zero risk, but there are many steps that can be taken to achieve a risk that is acceptable from a public health perspective. What surveillance measures are/should be built into a protocol?

Is there a way to avoid the problem of PERV transmission? For example, there is a line of MGH miniature swine that is believed not to transmit PERV. The committee may want to hear more about this at a future meeting.

Are there differences in the risk of infection from cellular vs. organ transplants?

- Response to infection and disease. How will investigators and the Federal government respond if transmission is detected and if disease occurs? Responsive measures will depend on how the organism is transmitted (saliva, semen, surfaces, aerosols, etc.). This may require long-term counseling and education for both recipient and contacts, as well as long-term monitoring.

Do current federal rules and guidelines deal with these questions adequately? Experience with human allografts indicates that diseases are transmitted during transplantation. At present there is no scientific basis for the safety of using primate tissues in xenotransplantation. This needs to be revisited as the science evolves.

- Screening. Is it possible to compile an exclusionary list of viruses to screen for, and how will we deal with newly identified porcine viruses?

### ***Ethical Issues***

- Risk assessment. What are the risks of infectious disease? We need an accurate and ongoing assessment of risks and how to minimize and control for them by measures judged to be sufficient. This should be at the top of any list of ethical concerns; the priorities among the others are open to debate.
- Risk/benefit balance. What is the foreseeable balance of benefits and risks to participants in clinical trials? This includes such issues as showing that rejection is sufficiently controllable, understanding the physiological function of animal organs in human recipients, identifying the population of patients most likely to benefit from xenotransplantation (in terms of length of survival and quality of life), understanding the probably emotional response of humans who receive animal transplants, and gauging the likely social response to xenotransplantation. Benefit-risk analysis should also include alternatives to xenotransplantation.

- Informed consent. Does xenotransplantation raise special problems with respect to obtaining the fully informed and voluntary consent of prospective recipients; third parties such as family members, close contacts, and health care workers; and their respective communities?

Is informed consent feasible/possible with a vulnerable, ill patient and a long, technical consent form (40 pages mentioned)? It would be useful for SACX to compile a list of the pertinent issues with regard to informed consent and disseminate that list to IRBs.

- Responsible oversight. Are current regulations and institutions adequate for the responsible oversight of xenotransplantation clinical trials? Should oversight be at the local or national level?
- Response to infection and disease. How will the public respond if transmission is detected and if disease occurs? Is public concern over this issue driven by science or by fear? There have been striking advances in hospital epidemiology and infection control over the past 25 years, yet society is increasingly concerned about (and intolerant of) medical errors and failures, as witness the language used in *To Err is Human* (IOM, 1999).
- Social justice. Can xenotransplantation be justified in terms of (1) the allocation of health care funds and (2) the availability of human and animal organs for all U.S. citizens.
- Natural law. Does xenotransplantation raise additional ethical and philosophical concerns with regard to (1) violations of natural law (e.g., blurring boundaries of human vs. animal) and/or (2) the moral status of animals vs humans.
- Impact on allotransplantation. Will excessive enthusiasm for xenotransplantation have a negative impact on human organ donations? Experience has shown that the possibility of payment for organ donation would decrease the supply of donated organs, while the advent of less-invasive procedures has increased the number of living kidney donors.
- National vs. international. What responsibility and accountability does SACX have to the public, nationally and internationally, in terms of education, accessibility and leadership? For example, is it enough to address what happens domestically, or should the committee also address the proliferation of “rogue xenotransplantation” operations abroad?
- Noncompliance. How should we deal with noncompliant recipients, and with the issues of autonomy and community that noncompliance would raise? Compliance is a criterion for access to renal transplants, but there has been no predictive study of how to evaluate the likelihood of compliance. A related question is whether alcoholics should be considered for Xenotransplantation. If there are no reliable studies, perhaps the committee should call for them.

## *Animal Welfare Issues*

- Moral standing of animals. From a theoretical perspective, does xenotransplantation invite a return to indirect moral standing of animals, wherein they are viewed as resources or tools for human use? Under the Animal Welfare Act amendments of 1985, and under current NIH policies, animals are seen as having direct moral standing, independent of (if not equal to) that of humans. Are the pain and suffering of “donor” animals to be considered in xenotransplantation, and if so, how?

Should exceptions be made to current guidelines in term of treatment for pain and suffering, endpoints other than death, approved methods of euthanasia, standards of care and housing? For example, closed herds in clean facilities are inherently restrictive and lack the environmental enrichment required by NIH rules. Farm animals and those used in agricultural research are specifically excluded from current standards, and the standards for pigs are different than those for nonhuman primates.

- IACUC expertise. From a practical perspective, do Institutional Animal Care and Use Committees have adequate expertise for reviewing xenotransplantation research? Should membership include a xenotransplantation specialist, where relevant?

## *Social and Economic Issues*

- Allotransplantation. How can we increase the supply of human organs for transplantation? Changes in criteria, as well as increased efforts in education and marketing, are possible. Presumed consent laws, which are common in Europe, could also increase supply.

How can we decrease the demand for organs? Preventive medicine and lifestyle changes could do a lot to decrease the need for medical care generally and transplants specifically.

- Cost. How will we pay for the costs of xenotransplantation? We currently spend \$4 billion per year on organ transplants, and estimates of future costs, should xenotransplantation become commonplace, range from \$20 billion to \$35 billion per year. These costs could have a dramatic effect on public funding for medical care and on private insurance (higher premiums, narrower coverage, increased number of uninsured).
- Healthcare policy. Where does xenotransplantation fit in the larger context of healthcare policy? Is the goal of that policy to extend life, to improve quality of life, or to provide basic medical care to all Americans? Forty-three million Americans under 65 have no health insurance, and 50 million have trouble getting access to even minimal care. Xenotransplantation may look like a luxury when the Federal Government can't find the funds to care for the uninsured.

## *Legal Issues*

- Liability. Who will bear the liability for the death of xenotransplantation recipients, the failure of the organ, or the transmission of a xenotransplantation-related infection? One model is the Court of Federal Claims, which administers a system of compensation for injuries associated with childhood vaccinations. Related questions have to do with responsibility for the continuing education of patients and contacts.

Are physicians responsible legally, as well as morally, to treat patients whom they suspect of having an unknown and potentially incurable disease as the result of an unregulated animal transplant?

- Privacy. What privacy issues are raised by the proposed archive of information and tissues from xenotransplantation recipients, their families, and health care workers? Protections will be needed against potential violation of Fourth and Fifth Amendment rights to privacy.
- Adequacy of rules and laws. FDA guidelines are more adaptable than regulations, but guidelines are nonbinding on industry; is that good enough, or are stricter rules and laws needed to manage the risks of xenotransplantation?
- Informed consent. Is informed consent feasible when it involves vulnerable recipients, indeterminate risks, and the implicit requirement for lifelong surveillance, which removes the right to withdraw and makes the agreement a binding contract?
- Noncompliance. Are current public health laws adequate to deal with the issues raised by noncompliant patients? At present, for example, it is illegal in most states to test for HIV without consent, but these laws are very specific and they don't apply to other retroviruses. On the other hand, there is precedent in AIDS for holding a noncompliant patient who has knowingly infected others.
- Property issues. Does xenotransplantation and the development of new forms of life raise new issues about patents and ownership of organisms, in addition to issues of cost and access?
- Surveillance and monitoring. Will healthcare workers and their professional organizations agree to extensive surveillance, including extended post-exposure monitoring? Does current employment law adequately address this issue?
- International regulation. If xenotransplantation emerges in nations where the technology is weakly regulated, or where facilities are inadequate, how can we promote an international regulatory mechanism to address risks? American patients are already going to (and returning from) xenotransplantation clinics in Mexico, Switzerland, Germany, and Russia.

Viruses do not respect national boundaries, but physicians could report such patient to public health authorities.

### ***Psychological Issues***

- Informed consent. How meaningful is informed consent when a terminal patient must read and agree to a 40-page document in the space of 30 minutes?
- Perception. How will the patient respond to the incorporation of a foreign organ? This issue has proven to be minor in allotransplants, but xenotransplantation is a new technology with a new set of concerns. For example, patients that receive an animal organ rather than a human organ might feel like a second-class citizen.

How will patients respond to the publicity attending Xenotransplantation and the changed reactions of friends and strangers? How will the patient's family perceive him after the transplant, and how will they deal with the uncertainty of the future and the demands of long-term surveillance? It was suggested that SACX might want to hear testimony from a number of patients about their experiences with xenotransplantation.

- Anxiety. How will the patient deal with anxiety about the length and quality of his life, financial demands, controlled sex, and long-term medication and surveillance? Should SACX recommend that there be research on this subject in conjunction with Xenotransplantation clinical trials?
- Reactions of healthcare workers. How will hospital staff deal with the dangers of xenotransplantation-related infections, and will their fears and misunderstanding have an impact on patients? What information and education programs are needed for health care workers?
- Neuropsychiatric effects. What are the neuropsychiatric effects of xenotransplantation-related viruses, antivirals, and immunosuppressants?

### ***Federal Agency Perspectives***

- What animal models are appropriate, feasible and valid for preclinical studies? What data should be submitted from animal trials? (FDA)
- What is the spectrum of risks from xenotransplantation, and are different controls appropriate for different techniques (coculture, cellular, organ transplant), or different duration of exposure, or different donor species? (FDA)

- How long should xenotransplantation recipients be followed, with what tests, and can surveillance be modified for different forms of xenotransplantation? How can researchers enforce compliance, or deal with noncompliance? (FDA)
- What patients should be excluded from participation (e.g., alcoholics, drug abusers, children, comatose)? (FDA)
- What level of public disclosure is appropriate? It would be useful for SACX to comment on the draft regulations that have been published in the *Federal Register*. (FDA)
- How can FDA do a better job of identifying potentially infectious agents? (FDA)
- What additional tests should be conducted on donor animals and human recipients? (FDA)
- How can FDA encourage community involvement, public education, and input from all interested parties? (FDA)
- Is there an adequate research base to support the scientific and policy decisions that must be made about xenotransplantation? (NIH)
- If additional federally funded research is needed, what incentives will be necessary to encourage new and established investigators to pursue research in this area? (NIH)
- What are the best roles for NIH, FDA and CDC in answering the questions raised by xenotransplantation? (NIH)
- What specific research will be needed to define the levels of risk, identify potential agents, and develop appropriate assays for xenotransplantation-related infectious diseases? (CDC)
- Do we need to expand efforts to investigate outbreaks in populations of source animals, so that we might detect novel infectious agents that could play a role in xenotransplantation? As new agents are discovered that may infect source animal populations, is retrospective surveillance of our existing xenotransplant recipients needed in an effort to attain some preliminary information on whether those specific agents pose a risk to humans? (CDC)
- What can be done to ensure equitable access to both allotransplantation and xenotransplantation for women, minorities and the poor? HHS Secretary Thompson has made organ donation a high priority and tasked the Division of Transplantation at HRSA to develop strategies in this area. The recently-formed Secretary's Advisory Committee on Organ Allocation (established under Secretary Shalala) will also consider issues of organ donation. (HRSA)
- How will xenotransplantation affect the supply of donated human organs? (HRSA)

- What are SACX's priorities? Of the issues identified in this meeting, which are the most important, and which will require prompt action? (OS)